LIFE TECHNOLOGIES & PUBLIC POLICY

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THE LIFE TECHNOLOGIES AND PUBLIC POLICY

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The Institute for Research on Public Policy
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Foreword

We live in an age of increasing mastery over human reproduction. Innovations, both scientific and technical, in medicine, genetics, and reproductive biology over the past fifteen years have delivered continuing increments of control over health and heredity, infertility and parenting, fetal development and birth. The behaviours and values at stake are vital to individuals and fundamental to society. What policies are appropriate for dramatic reproductive change in societies that are both democratic and morally pluralistic? Those charged with responsibility for the protection of individual rights and liberties and for the stability of the common good face a sensitive, difficult, and inescapable task.

In this study Drs. Roy and de Wachter offer an anatomy of the issues policy makers must face as they consider how artificial insemination, in vitro fertilization, surrogate mothering, prenatal diagnosis, and genetic engineering should enter and settle within Canadian society. The study is based on the principle that understanding the societal or policy issue requires a grasp of the scientific or technological innovation from which it arises. The focus is on the present, not on the distant future. The emphasis is on analysis of what policy makers must consider, not on recommendations about what they should do. As may be seen from the many commissions already established to consider these matters, actual policy will vary from nation to nation, and may even differ among various regions within a country.

The design of policy for innovations in the life sciences needs the collaboration of persons from many disciplines and professions. This book will merit the attention of doctors, scientists, lawyers, hospital administrators, governmental representatives, educators, and citizens at large. All are addressed, both personally and professionally, by the matters raised for study in this book.

A.R. Dobell
President

August 1986

Avant-propos

Nous vivons à une époque où la reproduction humaine fait l'objet d'une maîtrise croissante. Les innovations, à la fois scientifiques et techniques, réalisées au cours des quinze dernières années dans les domaines de la médecine, de la génétique et de la biologie de la reproduction ont assuré à l'homme un contrôle de plus en plus étendu sur la santé et l'hérédité, la stérilité et la fertilité, ainsi que sur le développement du foetus et la naissance. L'issue de cette évolution au point de vue des comportements et des valeurs est vitale pour les individus et fondamentale pour la collectivité. Quelles lignes de conduite les sociétés démocratiques et pluralistes doivent-elles adopter face aux changements qui bouleversent actuellement la fonction de reproduction? Ceux qui sont investis de la responsabilité d'assurer la protection des droits et des libertés individuelles ainsi que la stabilité de l'intérêt commun font face à une tâche délicate et ardue, mais inéluctable.

Dans la présente étude, les docteurs Roy et de Wachter tentent de cerner les enjeux inhérents au processus d'élaboration des lignes de conduite dont doit se doter la société canadienne en matière d'insémination artificielle, de fécondation in vitro, de transplantation de foetus à des mères d'accueil, de diagnostic prénatal et de sélection eugénique. Leur démarche lie la compréhension de ces enjeux à la connaissance préalable des innovations scientifiques ou technologiques auxquels ils sont associés. Offrant une perspective qui privilégie le présent aux dépens de l'avenir lointain, les auteurs ont préféré scruter les facteurs dont doivent tenir compte les décideurs relativement aux lignes de conduite à adopter, plutôt que de faire des recommandations sur le type d'interventions à effectuer. Comme l'ont démontré les divers comité créés pour étudier ces questions, les interventions pourront varier d'un pays à l'autre, et même présenter des différences entre les régions d'un même pays.

L'élaboration de lignes de conduite découlant des innovations au chapitre des sciences de la vie devra mettre à contribution des personnes représentant un vaste éventail de disciplines et de professions. Cet ouvrage intéressera les médecins, les scientifiques, les juristes, les gestionnaires d'hôpitaux, les commis de l'État, les éducateurs ainsi que les citoyens en général. Les questions qui y sont traitées les concernent tous, personnellement et professionnellement.

Rod Dobell
Président

Août 1986

The Authors

Dr. David J. Roy is founder and director of the Center for Bioethics of the Clinical Research Institute of Montreal. He was a member of the advisory committee that prepared a report on artificial insemination for Health and Welfare Canada, Health Protection Branch. In 1985 and again in 1986, he was one of Canada's three official representatives to the summit 'nations' international meetings on bioethics. He has served as consultant to doctors and health care professionals on ethical problems in medicine and clinical research, and now devotes most of his time to research on ethical issues in clinical medicine and biomedical science. He is Editor-in-chief of the Canadian-based international Journal of Palliative Care.

Dr. Maurice A.M. de Wachter is the director of the Institute for Bioethics, Maastricht, The Netherlands. Between 1978 and 1984 he worked at the Montreal Centre for Bioethics. As a consultant to the Montreal Children's Hospital, he was regularly involved in the ethics of prenatal diagnosis and genetic counselling. With the Association des Médecins de langue française du Canada, he developed a policy statement on prenatal diagnosis. He has published several articles on the relationship of ethics and public policy.

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Summary

The general public tends to reduce a new technology to its most startling feature. "Test-tube babies," for example, comes to stand for the reproductive technologies. A poorly understood catchword diverts critical attention from both the power and the limits of a new technology. This book offers an integrated presentation of the battery of techniques that make up the life technologies. The emphasis is on genetic engineering, prenatal diagnosis, and human reproduction.

A technology is major if it initiates changes that affect citizens in all walks of life on matters of high importance. A technology is revolutionary if it is able to bring about these changes in a short time. A revolutionary technology challenges traditional patterns of behaviour, governing value systems, and the institutions through which the common good is maintained and the public purpose is achieved. The genetic and reproductive technologies are major and revolutionary. Their challenge creates the need for a flexible response that facilitates transition and curbs the hasty implementation of ideas that will invite reversal. This book explores the issues to be resolved in developing such a response.

The genetic and reproductive technologies are here to stay. Since the late 1960s, the question of applying them to human beings has been raised repeatedly. Speculative forecasts quickly ceded the field to successful application and growing public demand. This is true for prenatal diagnosis and artificial insemination. The same process is now occurring with in vitro fertilization and embryo transfer. Genetic therapy and novel variations of the reproductive technologies, such as surrogate motherhood, may well follow a similar path in the near future.

An earlier publication of the Institute for Research on Public Policy addressed the development and industrial exploitation of microbes in pharmaceutics, mining, and the food industries.[1] It is now time to examine current and future applications of biomedical technologies to human beings.

The present study is a preparation for policy design. It does not attempt to draft specific policy proposals, but rather to evoke public reflection. It has been written to focus the attention of policy makers on developments and practices that require policy decisions.

It is difficult to devise a policy for a technology that has not yet been applied; experience is necessary to distinguish important from peripheral concerns. Without that experience, anxieties are often unrelated to risks, and expectations bear little relation to potential. This book identifies the real issues that have emerged from the experience so far acquired with prenatal diagnosis and the reproductive technologies. Genetic therapy is not yet available for application to human beings, but the rapid advance of science toward this kind of therapy raises unique issues meriting public attention now.

The framework of discussion in Chapter 1 derives from the distinction between a reproductive technology still in its early stages of development and one that is already successfully applied to human reproduction. The general survey method employed allows for ample discussion of technologies not selected for detailed analysis. Artificial insemination and in vitro fertilization were chosen as the main topics because each technique is now used in human reproduction, and each requires public policy decisions on a range of issues. Chapter 1 identifies these issues.

Chapter 2 evaluates the current practice of prenatal diagnosis, a new reproductive technology that has grown dramatically since the early 1970s. In 1971, for example, the Genetics Clinic at Toronto's Hospital for Sick Children performed six amniocenteses (that is, the sampling of amniotic fluid by the insertion of a hollow needle) for the detection of affected fetuses. By 1978, the number of amniocenteses performed in that hospital had reached 776. These figures are representative for most centres throughout North America, and they reflect the rising demand for this new technology, which has at least five major techniques at its disposal.

As the interaction between genes and environment in health and disease becomes better understood, medicine is developing a genetic paradigm, or model of disease, in which prevention dominates, diagnosis is growing exponentially, and therapy is on the horizon. The field of prenatal diagnosis needs policy guidelines for access to services, diagnosis of indications, the communication and use of results, and receiving genetic counselling. The policies now practised vary from centre to centre, and for this reason, the making of policy may soon become a matter of concern, both nationally and internationally.

Chapter 2 also unveils policy issues that stem from practices and techniques. The sections on the state of the art and on indications and goals of prenatal diagnosis, for example, generate their own specific policy questions. The issues requiring public policy decisions, examined in the last major section of the chapter, should draw the attention of policy makers, those on whom society relies to strike a fresh balance among conflicting forces.

Chapter 3, which deals with genetic engineering and genetic therapy, rests on the assumption, amply demonstrated throughout the debate on recombinant DNA, that the social issues emerging from the new genetics will be misconstrued and related policies misdirected if the technologies are not accurately understood. Genetic engineering encompasses more than the techniques of recombinant DNA. It is a complex technology comprising powerful technical achievements and skills. Taken together, these techniques give scientists the nascent ability to read, correct, and rewrite nature's genetic messages. This power leads directly to some of the most critical issues raised by the new genetics. Another set of issues emerges when current and future genetics projects impinge on differing expectations and anxieties.

The description of the technologies in Chapter 3 carries an implicit admonition to policy makers who want to get quickly to the "bottom line": anyone charged with public responsibility for matters arising from applications of genetic engineering cannot simply bypass a basic understanding of the technology. This understanding is a prerequisite for the judicious evaluation and resolution of social issues arising from the new genetics.

The final chapter analyses four issues that pervade discussions of the technologies examined in this study. Value conflicts and divergent philosophies of life create particularly difficult challenges for policy makers. Two further issues arise from the rapidity of advances on many scientific and technological frontiers. If knowledge is power, how can a democratic society guard against the concentration of power in the hands of a knowledgeable elite? How can we attain the kinds of public information and education required for public participation in decisions about innovative applications of science and technology? A fourth issue focuses attention on the opportunities and possible dangers of an emerging connection between universities and industrial corporations in promoting pure and applied research in the life sciences.

Note

1. Pierre Sormany, *Les micro-esclaves : vers une bio-industrie canadienne* (Montreal: Institute for Research on Public Policy, 1979).

Abrégé

Le grand public a tendance à réduire toute nouvelle technologie à son aspect le plus saisissant. Par exemple, les "bébés-éprouvettes" en sont venus à représenter l'ensemble des technologies de reproduction. Ainsi, un mot à la mode et mal compris nous empêche de saisir judicieusement tout le pouvoir, mais également toutes les limites, que recèle une nouvelle technologie. Ce volume propose une vue d'ensemble des techniques que forment les technologies de la vie. Cependant, l'emphase porte sur l'ingénierie génétique, le diagnostic prénatal et la reproduction humaine.

On dit d'une technologie qu'elle est majeure si elle donne naissance à d'importants changements affectant toutes les couches de la société. Cette même technologie devient révolutionnaire si ces changements surviennent dans un bref laps de temps. Une technologie révolutionnaire défie les modèles de comportement traditionnels, les systèmes de valeurs qui les régissent et les institutions chargées de maintenir le bien commun. Les technologies associées à la reproduction humaine et à la génétique sont majeures et révolutionnaires. Le défi créé par ces technologies a fait naître le besoin de réponses souples et capables de faciliter cette transition et de mettre un frein à l'implantation hâtive de projets qui par la suite seront mis de côté. Ces pages examinent les enjeux qu'il faudra considérer lorsque viendra le moment de proposer de telles réponses.

Les technologies de la reproduction et de la génétique sont ici pour y rester. Leurs applications à la race humaine ont été soulevées à plusieurs reprises, depuis la fin des années 60. En fait, la spéculation a rapidement fait place à plusieurs réussites et à une demande croissante de la part du grand public. Ainsi en est-il de l'insémination artificielle et du diagnostic prénatal, et on remarque le même phénomène pour la fertilisation *in vitro* et le transfert d'embryon. Il se peut fort bien que la thérapie génétique et les nombreuses variations des technologies de la reproduction, telles que les "mères d'emprunt", suivent le même parcours au cours des prochaines années.

Déjà, en 1979, une des publications de l'Institut de recherches politiques portait sur le développement et la commercialisation des microbes dans l'industrie alimentaire, pharmaceutique et minière[1]. Le moment est maintenant venu d'examiner les applications futures aux êtres humains des technologies biomédicales.

Cette étude est un document de base en vue de l'élaboration de politiques publiques. Son rôle n'est pas de proposer des politiques, mais de susciter la réflexion chez les décideurs publics et d'attirer leur attention sur les innovations qui nécessitent une réglementation.

En fait, il est difficile de concevoir de telles politiques pour une technologie qui n'est pas encore en application : il faut de l'expérience pour distinguer les problèmes imminents des inquiétudes éloignées. Sans cette expérience, les craintes sont disproportionnées risques, et les attentes n'ont aucun rapport avec les possibilités. Ce livre identifie les véritables problèmes qui, à ce jour, émergent en raison de l'expérience acquise avec le diagnostic prénatal et les technologies de la reproduction. La thérapie génétique ne s'applique pas encore aux êtres humains, mais cette science évolue si rapidement que les problèmes bien spécifiques qu'elle soulève méritent notre attention dès maintenant.

Le cadre de discussion du premier chapitre provient de la distinction entre une technologie de reproduction qui en est à ses premiers stades de développement et une qui a été mise en application avec succès auprès d'êtres humains. La méthode du survol employée dans ce chapitre permet une plus ample discussion des technologies que l'on n'a pas choisi d'analyser. Notre choix s'est donc arrêté sur l'insémination artificielle et la fertilisation *in vitro* parce que ce sont deux techniques utilisées couramment et que chacune requiert la mise en application de politiques publiques sur de nombreuses questions. Le premier chapitre les identifie.

Le deuxième chapitre évalue différents aspects du diagnostic prénatal, une nouvelle technique de reproduction devenue courante et qui a augmenté de façon dramatique depuis le début des années 70. Prenons l'exemple de la clinique de génétique du Toronto Hospital for Sick Children. En 1971, on y pratiquait six amniocentèses (insertion d'une aiguille pour en retirer le fluide amniotique) afin de détecter les foetus atteints d'anomalies génétiques, alors qu'en 1978 ce nombre était passé à 776 amniocentèses. Ces chiffres sont représentatifs de plusieurs cliniques en Amérique du Nord. Ils reflètent la demande croissante pour cette nouvelle technologie qui dispose d'au moins cinq méthodes de diagnostic.

À mesure que l'interaction entre les gènes, l'environnement et la maladie est mieux comprise, la médecine développe un paradigme génétique, un modèle de maladie, où la prévention domine; le diagnostic s'accroît de façon exponentielle et l'on voit poindre de nouvelles thérapies. Tout le domaine du diagnostic prénatal nécessite la mise en application de lignes de conduite pour déterminer l'accès au service et les indications, la divulgation et l'utilisation des tests, et la dispensation de conseil génétique. Les politiques mises en application varient d'un centre à l'autre et, pour cette raison, l'élaboration de telles politiques deviendra bientôt une préoccupation majeure tant au niveau national qu'international.

Dans ce chapitre, on soulève le voile sur les enjeux issus de ces pratiques et techniques qui nécessitent la mise en application de politiques publiques. Par exemple, les sections qui portent sur l'état de la question et sur les indications et les buts du diagnostic prénatal contiennent en soi des questions de politiques très spécifiques. Les questions nécessitant des décisions d'ordre public sont examinées à la fin du chapitre. Elles devraient retenir l'attention des décideurs publics, car c'est sur eux que la société se fie pour établir un nouvel équilibre parmi tant de forces conflictuelles.

Le troisième chapitre porte sur l'ingénierie génétique et la thérapie génétique. Il repose sur l'hypothèse, amplement démontrée lors du grand débat sur la recombinaison de l'ADN, que si ces nouvelles technologies ne sont pas bien comprises, les problèmes sociaux qui en découlent seront mal interprétées et les politiques publiques mal conçues. L'ingénierie génétique ne se limite pas aux techniques de recombinaison de l'ADN. C'est une technologie complexe qui a déjà à son actif des réussites pleines de pouvoirs et de promesses. Dans leur ensemble, ces techniques donnent aux scientifiques le pouvoir, sans précédent, de lire, corriger et même réécrire l'héritage génétique. C'est ce pouvoir qui est à la base de tous les problèmes que la nouvelle génétique soulève. Dans un autre ordre, de graves problèmes surgissent également lorsque les visées de certains projets se heurtent à nos attentes et nos anxiétés.

La description de ces technologies dans le troisième chapitre comporte un avertissement implicite pour les décideurs publics qui voudraient en venir rapidement au fond du problème. Toute personne chargée d'élaborer des politiques publiques pour les techniques relevant des applications de l'ingénierie génétique ne peut se permettre de contourner les notions scientifiques fondamentales de cette technique. Pareille démarche constitue le préalable d'une évaluation et d'une résolution sensées des enjeux sociaux découlant des progrès de la génétique.

Enfin, le dernier chapitre analyse quatre questions en jeu que l'on retrouve tout au long de cette étude dans les discussions sur les nouvelles technologies. Les conflits de valeurs, et les différentes philosophies de la vie créent des défis particulièrement difficiles aux décideurs publics. L'accélération du rythme des découvertes scientifiques et technologiques soulève deux autres questions. Si connaissance égale pouvoir, comment pouvons-nous dans une société démocratique nous prémunir contre le danger d'une concentration du pouvoir entre les mains d'une élite instruite? Comment pouvons-nous fournir au grand public l'information adéquate de sorte qu'il puisse participer activement aux discussions et aux décisions portant sur les innovations scientifiques et technologiques? Enfin, le dernier point qui est soulevé traite des opportunités et des dangers possibles suite aux ententes entre les universités et les corporations industrielles en vue de promouvoir la recherche pure et appliquée dans les sciences de la vie.

Note

1. Pierre Sormany, *Les micro-esclaves : vers une bio-industrie canadienne* (Montréal, L'Institut de recherches politiques, 1979).

Chapter 1:

Technology in Human Reproduction

David J. Roy

> Few if any developments in biological technology have influenced the life of the common man and woman more, in this century, than the growing power to control human reproduction. . . .[1]

Introduction

Why should those who influence decision making in Canada concern themselves with today's applications of new technologies to human reproduction? A quite prevalent belief is that decisions about having or not having children, as well as choices about how to have or avoid having them, are private freedoms to which public policy does not pertain. This belief starts with a truth nearly everyone holds in one form or another. Who would deny that human reproduction is best achieved by a profoundly personal and private act? Hence, it is identified as an individual freedom. The belief ends in a generalization: human reproduction is *exclusively* a personal and private act. This view overlooks a truth, however, that, upon sober reflection, almost everyone would accept. Would anyone deny that human reproduction is an eminently social act? Having children has social and public consequences. It would be naive, therefore, to assume that when the methods of human reproduction begin to differ in startling ways from sexual intercourse, to which reproduction has been bound since the dawn of humankind, such profound changes in the manner of conception of future members of society would not generate a new group of public concerns and problems. Such problems are with us already, and we can expect many more.

Although artificial insemination by a donor (AID) has been practised in North American and European societies for many years, a wide range of attendant problems, both legal and social, still await solution. Innovations using AID, such as surrogate and host motherhood, have only recently been attempted. They already present legal and social quandaries that will tax the imagination of policy makers for years to come. Laboratory or in vitro fertilization (IVF) of human ova is another advance toward a more complex technology that could soon permit greater control over human reproduction than has ever before been possible.

These new reproductive technologies offer new controls and power precisely because they break with the biological roots of parenthood. A biological necessity for man-woman sexual intercourse, with all its implications for humanity, has ensured a common origin for human beings, however widely the patterns of marriage, parenthood, and family have differed from culture to culture and from generation to generation. This common origin has served as an unquestioned communal and social shield against novel forms of parenthood. It has functioned as the apparently unchangeable basis for the social ethics and laws devised to regulate society's key institutions of marriage, parenthood, and family.

Applications of new technologies to human reproduction have created a dramatically new situation. These applications, those already available and those in the process of development, may well permit:

- novel solutions to the problems of male and female sterility
- socially revolutionary forms of pregnancy
- powerful instruments of therapeutic intervention in early human life
- effective techniques for the practice of eugenics (the production of improved offspring by controlling the qualities they inherit)
- the construction of human embryos for research and experimentation

These new technologies deliver the power to do things that have never before been possible with human reproduction. In turn, these new abilities raise moral, social, legal, and philosophical-theological questions. Scientists need not—perhaps should not—undertake every new application that they can technically achieve. This chapter, as well as the entire book, will focus on the issues that are properly questions for public policy.

The issue of control over human reproduction is making its way into case law. In *Curlender* v. *Bio-Science Laboratories*, a lower court in California permitted recovery by the child in one of an increasing number of "wrongful life" cases. A key issue in this case was the laboratory's failure to detect that the parents were potential carriers of Tay-Sachs disease. The court's opinion indicated a possibility of legally recognizing a defective child's right in law to sue parents for a defective existence that could have been avoided. The corollary is parental liability, which would have been an unthinkable concept several years ago, before the attainment of the ability to control reproduction. The scope of that control is now discussed in such terms as "preconception diagnosis" of parents, "prenatal diagnosis" of the fetus, and "negligent exposure" of the fetus to harmful conditions. These terms identify only the beginnings of a range of reproductive controls that is likely to become much more extensive.

Technological control creates the need for public policy. In considering a hypothetical case of parents deciding to go ahead with a pregnancy even after being warned of the probability of having a defective child, the California court saw "no sound public policy which should protect those parents from being answerable for the pain, suffering, and misery which they have wrought upon their offspring."[2] Others, however, have objected to the position taken by this court. Their objections are based on the likely social consequences for families and pregnant women should a normal birth come to be viewed as the governing value of reproductive ethics.[3]

Those considering public policy cannot afford to give one-sided emphasis either to the promises or to the problems – or even the perils – of a new technology. They must devise adequate preparations for all foreseeable possibilities. The reproductive technologies offer both the opportunity for making positive advances and the possibility of undertaking regrettable projects, as well as chances for creating mischief.

The Reproductive Technologies: A Survey

The term "reproductive technology" is frequently used without formal definition to cover at least the following procedures:

- artificial insemination by the husband (AIH) or by a donor
- in vitro fertilization of human ova
- embryo transfer
- cryobanking (the freezing and banking of sperm and fertilized ova)
- sex selection
- external gestation (the use of an artificial placenta and an artificial uterus
- cloning

These technologies are not all at a stage of development advanced enough for serious public policy discussion.

One important characteristic of the procedures covered by the term "reproductive technology" is that they do now, or may one day, permit the partial or total bypass of sexual intercourse and uterine gestation for pregnancy. A second characteristic is that these procedures, alone or in combination with other techniques such as those of prenatal diagnosis, expand the abilities to monitor, manipulate, modify, and control the events of human reproduction. Third, these technologies permit reproductive methods or projects that could not be undertaken by the natural process of sexual intercourse.

Artificial Insemination

Artificial insemination (AI), particularly with donor semen, has been used for many years and in various parts of the world. It is frequently difficult to obtain accurate statistics from countries or regions for the number of children conceived by AID over specific periods of time. Some researchers have estimated that about 250 000 persons living in the United States have been conceived by AI and that 2000 to 10 000 such conceptions occur annually.[4] The Centre d'Etude et de Conservation du Sperme Humaine (CECOS), the centre of a network of sperm banks and AI services in France, reported 7160 AID requests accepted and 1852 pregnancies achieved for the period 1973-1978.[5] Canadian practitioners have calculated that from 1968 to 1978 at least 1500 births occurred in Canada as the result of artificial insemination.[6] Nearly every country in which AID is practised has noted steady increases in the number of requests for the procedure in the past few years.

In Vitro Fertilization and Embryo Transfer

Human reproduction by IVF and embryo transfer, though more recent and not yet as widely practised as AID, is used in more and more clinics throughout the world. The first successful birth by these methods, that of Louise Joy Brown, took place in England in July 1978. Since then, more than 1000 babies have been born from IVF and embryo transfer. There are now more than 200 IVF programs established in various countries. Given the high numbers of potential candidates and requests for pregnancy by these procedures, they will undoubtedly become more widely practised as technical experience accumulates and the efficiency of embryo transfer increases.

Cryobanking of Human Sperm and Ova

Since the early 1950s, human sperm has been successfully frozen, stored, thawed, and subsequently utilized. These procedures are regularly used in conjunction with AIH and AID in many countries. About 12 commercial and university-based sperm banks exist in the United States, 15 in France, and fewer than 12 that are worthy of note throughout the rest of the world.[7]

The human banking of ova, the freezing and preservation of unfertilized human eggs, is not currently being done. There are, however, indications of a greater interest in perfecting techniques for the cryopreservation of human zygotes (fertilized human eggs). Fertilized eggs of several mammalian species, particularly of the mouse, rat, rabbit, sheep, and cow, have been successfully frozen, thawed, implanted, and brought to birth. In February 1982, the press reported that Dr. Patrick Steptoe and Dr. Robert Edwards planned to set up banks of frozen fertilized eggs or embryos and quoted an article the two physicians published earlier: "The storage of human pre-implantation embryos at low temperatures could be valuable in clinical practice for the cure of infertility and possibly to avert inherited defects in children."[8]

The same article mentioned that doctors in Melbourne, Australia, have already frozen and thawed 12 embryos.[9] A small number of pregnancies have already been achieved by implanting previously frozen human embryos. Live births resulted in at least two instances, and the babies showed no detectable defects. The implantation could be into the womb of a woman from whom the egg did not originate, setting the stage for "prenatal adoption."

The status of frozen and stored human embryos poses major legal, social, and moral issues. Reports in the summer of 1984 that two frozen human embryos were in storage in Melbourne, Australia, after the couple responsible for them, Mario and Elso Rius, died in a plane crash, provoked international discussion about the right to life and inheritance of such embryos.

Sex Selection

In an editorial in 1974, *The Lancet*, a British medical journal, cited two techniques indicating "that predetermination of sex of offspring, through artificial insemination with a purified sample containing the required sperm type, may be just around the corner."[10] Although no simple and highly reliable means of selecting the sex of offspring before conception is yet available, one may, without question, expect such a method in the near future. Estimates vary on what the demand will be for such a method of sex selection when the technique does become available. The sex of a fetus can now be ascertained with currently practised methods of prenatal diagnosis. Fetuses have been aborted because, being male, they ran a 50 per cent risk of having Duchenne's muscular dystrophy, one of the diseases that is linked to the X chromosome. The literature on medicine and ethics has addressed the practice of aborting fetuses, not because they were in risk of disease, but simply because they were not of the sex desired by the parents. Because selection of sex before conception satisfies several objectives, it is possible that it will be a common phenomenon in Western society when a simple, reliable method becomes available. It is also likely that when such a method comes into use, "the individual, the physician, and society will be confronted with new problems."[11]

External Gestation

The viability of a fetus, that is, its ability to survive and thrive outside the uterus, varies with the development of existing technologies for the support of new-born babies. Some premature babies can now be sufficiently supported outside the womb after a gestation period of 24 weeks to permit their normal development.

With the techniques of IVF, a fertilized human egg – a "zygote" or "pre-embryo" – is kept alive and cleaving (process of cell division) for several days until an attempt is made at implantation in a uterus. In its 1979 *Report on Human In Vitro Fertilization and Embryo Transfer*, the Ethics Advisory Board of the U.S. Department of Health, Education, and Welfare (DHEW)[12] concluded that it would be ethically acceptable to undertake research involving human IVF and embryo transfer, provided that, among other conditions, "no embryos will be sustained *in vitro* beyond the stage normally associated with the completion of implantation (14 days after fertilization)."[13] This stricture assumes that the technical ability exists today to keep a human embryo alive for several weeks in the laboratory and outside a uterus (though Dr. D. Petrucci claimed, as early as 1959, to have kept two fertilized human eggs alive in a laboratory, one for 29 and one for 59 days).[14]

The period of intra-uterine fetal development that cannot presently be replaced by the techniques used for IVF and premature baby support remains a target for technical ingenuity. Though work has been under way at least since the late 1960s on the development of an artificial mammalian placenta and uterus, neither is currently in the final stages of design and development, let alone available for experimental work on human fetuses. It is far from easy to mimic technically the mammalian placenta. As explained in the book *Utopian Motherhood,*

> The high hurdle along the road to an effective artificial womb is that marvelous and mysterious combination of maternal and fetal tissues known as the placenta. It acts as a selective filter passing certain substances, amino acids, vitamins, oxygen, and sugars from mother to the fetus, but acting as a filter to screen out many proteins, blood cells, and other substances which might trigger an immune rejection in the embryo or cause it harm. It took scientists five years of intensive experiments to understand the physiological processes involved in the simple diffusion of oxygen and carbon dioxide across the placental barrier.[15]

A functioning artificial placenta and uterus would enhance fetal observation and monitoring and could prove to be scientifically, medically, and socially revolutionary. Under these conditions, fetal medicine and surgery could advance more rapidly than is likely now, even though quite remarkable therapeutic interventions have been performed on the fetus within the womb. In the context of totally extra-uterine gestation, the concept and law of abortion would inevitably undergo significant change. The short- and long-term social and cultural effects that would accumulate from a technology that could completely free women from pregnancy are imaginable, even if difficult to identify with precision and certitude. Although a functioning and marketable artificial placenta and uterus will probably not be available for many years, the difficulties that must be overcome to ensure this development are primarily technical and may not be insuperable.

Cloning

The cloning of a human being would typically involve the implantation of the nucleus of a 46-chromosome cell from an already-existing human being into a human egg. Theoretically, this could be done with prior removal of the egg's 23-chromosome nucleus or with subsequent removal of a fertilized egg's two pronuclei. If these steps of nuclear transplantation were successful, the child-to-be would be genetically identical to the identical twin of the already existing human being from whom the 46-chromosome cell had been taken.

No published scientific evidence justifies claims that a human being has ever been cloned, but this says nothing about how imminent the first success at producing a human clone might be. The possibility of cloning human beings should be taken seriously for several reasons. Scientists have already successfully cloned frogs and mice, and they can, in all likelihood, apply the microsurgical techniques involved in the nuclear transplanting of these clonings to the human ovum and cell nucleus without major additional difficulty. Necessary accompanying techniques for a human cloning, IVF and embryo transfer, are now accomplished facts. Furthermore, study and experimentation with the early human embryo is expected to be a major research activity for at least several years to come.

The claim that the prospect of cloning human beings should be given serious consideration does not imply that this prospect should be approved. The consideration is necessary because of advances made with microsurgical techniques of nuclear transplantation. The apparent success achieved by Karl Illmensee and Peter Hoppe in transplanting the nuclei of mouse blastocyst (embryonic) cells into fertilized and enucleated mouse eggs brings these techniques into the mammalian domain and a step closer to the domain of human beings.

It would be premature, however, to leap from the Illmensee-Hoppe experiment to the popularly imagined project of creating identical copies of an existing adult. Illmensee and Hoppe transplanted the nuclei from cells, not of an adult mouse, but of a mouse blastocyst. In other words, the donors for the nuclei used in the cloning were fertilized mouse eggs that had developed through only several cell divisions after fertilization. The baby mice that resulted from this process of nuclear transplantation and subsequent embryo transplantation into the womb of a female mouse were twins, so to say, not of some adult mouse, but of the mouse zygotes that would have developed from the fertilized eggs that were enucleated to house the transplanted nuclei.

There is little scientific evidence that the nucleus of an adult mammalian cell can be transplanted and brought to develop into a normal offspring. As Illmensee and Hoppe emphasize,

> one should bear in mind that it has not yet been possible to produce an adult frog derived from the transplanted nucleus of a differentiated adult cell. The extent to which nuclei from differentiated cells can be reprogrammed after injection into amphibian eggs is still unknown, nor do we understand the processes involved in nuclear differentiation as the developing

> organism becomes more and more specialized in structure and function.[16]

These remarks may reduce any heightened expectations of human cloning, but Landrum Shettles's claim may raise them again. Shettles claims that he has isolated nuclei from human spermatogonial cells and microsurgically injected them into enucleated human ova. In three cases of successful transfer of nuclei, the ova containing these transplanted nuclei divided normally up to the morula stage (when the fertilized ovum normally enters the uterine cavity). "There was every indication that each specimen was developing normally and could readily have been transferred in utero by the catheter technique cited in 1971," Shettles recorded.[17]

In this report, largely unnoticed and hardly discussed, Settles is apparently claiming to have achieved a successful transplantation of a human adult-cell nucleus with successful post-implantation cleavage similar to the results Illmensee and Hoppe achieved with the mouse nuclei. The difference is in Shettles's termination of the experiment without attempting to implant the dividing cells into an appropriate uterus. On the basis of the claims cited above, had Shettles attempted to transfer these cells to a uterus and succeeded, a baby might have resulted who would have been genetically identical to the man from whom the spermatogonial cells had been taken to obtain the nuclei for transplantation.

One cannot reasonably claim that earlier discussions of the ethical and social consequences of human cloning were premature. It is never too early to open discussion of a technology that appears likely to be developed and likely to modify profoundly a traditional pattern of behaviour, in this case, reproductive behaviour. This method of reproduction would differ profoundly from the sexual reproduction that takes place without sexual intercourse in the process of IVF. In sexual reproduction, biological parents each contribute 23 chromosomes for the building of the first 46-chromosome cell that constitutes the beginning of a human being. Cloning would dramatically change our notion of parenthood.

Though the cloning of human beings may not yet merit serious public policy design, and though it may be difficult to identify realistically and to discuss the applications and social consequences of cloning, it would be naive simply to set this project aside as the product of a science-fiction imagination. The current state of the art and the potential social consequences of human cloning, should it ever be successfully attempted, do not justify cavalier attitudes. As a scientist in the American magazine *Atlantic* pointed out, "The nature of the bond between parents and their children, not to mention everyone's values about the individual's uniqueness, could be changed beyond recognition. . . ."[18]

Why AID and IVF Are the Subjects of Public Policy Analysis

The distinction between an emerging and an existing technology governs the scope of attention given to topics throughout both this chapter and this book. Public policy analysis, on the one hand, is particularly appropriate for technologies that already are, or will soon be, realities. Early, wide-ranging, and broadly philosophical considerations of emerging technologies are necessary to prepare both the general and the professional communities for making the major decisions, the probable changes, and the adaptations these technologies will require. These early explorations are, however, necessarily hypothetical and speculative.

Public policy recommendations, on the other hand, serve as guides for actual decision and action. They are designed to be implemented. They presuppose the existence of real social issues. They require a precise identification and analysis of real opportunities and problems that are now generating social demand and public controversy.

AID and IVF with embryo transfer—as well as certain applications of these technologies, such as surrogate motherhood and experimentation with the human fertilized egg—now require public policy recommendations. Consequently, the following sections of this chapter focus on the issues raised by applications of these two major reproductive technologies. The technologies associated with the terms "sex selection," "external gestation," and "cloning" are not yet sufficiently developed to be applied in Canada.

The technologies under discussion raise issues that one can label as scientific, medical, legal, ethical, philosophical, theological, and social. Some procedures, such as abortion, require discussion under each of these labels. Though some people would like to confine abortion to the domain of moral or religious matters, it has become a major and recurrent issue for public policy debate in North America and other parts of the world during the past few years. Other scientific issues have followed a similar path, such as recombinant DNA, which moved very rapidly from the domain of scientific discourse into the arena of legislative proposals in the U.S. Congress.

Artificial Insemination
A Synopsis

Artificial insemination of women, whether with their husbands' sperm or the sperm of donors, has been both practised and professionally reviewed for nearly a century. The first recorded pregnancy and birth of a child conceived by AIH, which took place in England in 1790, is credited to Dr. John Hunter. Several sources mention 1884 as the date of the first successful AID pregnancy.

AI has also generated an extensive literature reaching back into the last century and across several countries. F. Déhaut's classic work was published in Paris in 1865; it was followed by the writings of J. Girault, published in Paris in 1869, and of J.M. Sims, published in the United States in 1869. A monograph from Russia written in French, E. Iwanoff's 1907 study of AI in mammals, is credited with having "introduced artificial fecundation as a practical, useful procedure in stock breeding and reexcited interest in the medical profession for its use for humans."[19]

The literature on AI is not restricted to monographs and articles by individual professionals. The Feversham[20] and Peel[21] reports from England are two examples of official and wide-ranging public inquiries into the legal and social aspects of the subject. The Canadian Minister of National Health and Welfare established an Advisory Committee that issued a report in 1982, *Storage and Utilization of Human Sperm*.[22] This *report* and current practice studies, such as the one by Curie-Cohen, Luttrell, and Shapiro, document recurrent attempts to identify unresolved problems relating to AID and to improve professional performance and service.[23] The first International Symposium on Artificial Insemination and Semen Preservation, held in Paris in April 1979, produced a multidisciplinary report of more than 600 pages, containing articles from 135 contributors.[24]

Despite the amount of time and the quality of professional consideration recently devoted to AID, policy makers still have not adequately resolved some of the major issues pertaining to this technology. One contributor to an American medical journal commented:

> There is much talk today about the "new biology" and its impact on the practice of medicine. Techniques for modifying behavior and "creating" new life, not yet fully developed, are already viewed by many as threats to the traditional role of medicine. The application of these emerging technologies, it is said, will generate a

> series of profound ethical, legal, and social problems for the medical practitioner as well as for the larger social community. While such claims may well be valid, it is a fairly old medical technology, one that can be traced back centuries, which has created for the physician and his patients an unsatisfactory and, in some cases, unhealthy situation. I am referring to artificial insemination. . . .[25]

This statement from 1974 is still applicable to artificial insemination in Canada as well as in the United States. The unresolved issues of AID will only become more complicated – and harder to resolve – as the newer reproductive technologies come to be used more widely in North American society. George J. Annas, a renowned commentator on contemporary matters of law and medicine, made this point very strongly: "We need a set of agreed-on principles regarding artificial insemination by donors and surrogate mothers – both technologies currently in use – if legislation on in vitro fertilization and embryo transplant is to have a reasonable chance of doing more good than harm."[26]

The unresolved questions raised by AI are not all properly topics of public policy. The following issues, however, do qualify for the clarification and regulation that an adequate public policy should offer. They are not listed in order of priority.

Insufficient Knowledge about AID

The Curie-Cohen study of AID, carried out in the United States, maintains that insufficient knowledge about the practice makes it difficult to establish uniform policies: "Despite the general interest in the subject, little is known about its scope or its current methods. Even authorities in the field find the search for vital statistics frustrating. Knowledge of national practices is necessary to establish uniform policies for this procedure, particularly as these policies bear on its genetic consequences.[27]

What sort of specific, verified knowledge is needed and for what purposes? A *Lancet* editorial mentions the assertion of some physicians that in England "demand has outstripped supply and . . . further expansion is urgent."[28] How can that claim be evaluated and acted upon in the context of a national health service when "there is no knowing the actual increase – because many practitioners work in clandestine fashion and because there may be no medical involvement at all?"[29]

Few studies, if any, are available on the psycho-social consequences of AID for practitioners, donors, donor families, recipient families, and the children born by this method. The same *Lancet* editorial emphasized the dearth of specific studies in these areas, "the most neglected by research, and yet perhaps the most important."[30]

The Advisory Committee Report mentions possible "psychological traps" and identifies some of the many unanswered questions:

> There is virtually no information on the variety of emotions and attitudes that must occur among young men who become sperm donors. Is the donor fearful of disclosure of his identity? Is it correct to assume that donors are generally motivated by unselfish desire to help the infertile couples? Donors and the recipient family require competent counselling and the education of both would be assisted by more information about the process.[31]

What does "competent counselling" mean? The *Lancet* editorial mentions the use in Denmark "of a multidisciplinary infertility team who are in frequent touch with clients before and after all procedures."[32] It admits, "We do not yet know however whether such joint counselling leads more readily to the stage of parental acceptance where the child is 'we'—our child, the incarnation of 'we'—than will the advice of a particular physician."[33]

Many factors militate against carrying out the kinds of studies so many people believe to be required. The factors may be technical; for instance, measuring techniques may be inadequate or the population insufficient to achieve valid results. The factors may also be ethical: How can such studies be done if confidentiality and family tranquillity are to be preserved?

The conclusions of the Advisory Committee report are somewhat paradoxical: The indications are that AID is a procedure with positive results, but in truth, no one really knows. This situation seems unlikely to change in the foreseeable future. . . . While the difficulties of conducting long-term studies appear insurmountable we believe that such studies are needed so that the practice of AID may be carried out with a better understanding of both the benefits and the risks."[34]

The *Lancet* editorial view establishes a more definite connection between the need for studies and the need for standards:

> Clearly more work on these and other psycho-social aspects of AID is needed to provide guidelines that will

> enable practitioners to maintain standards, to ask for more National Health Service attention to AID, and to bring pressure on colleagues whose conduct falls short. Already there are clinics which tout for business in the popular press; and some practitioners provide AID services for single women, for lesbian couples, and for people with psycho-sexual difficulties – when there is clear evidence that children brought up in such circumstances can be seriously disadvantaged.[35]

Standards

In the United States, AI has been called "a cottage industry on the verge of mass marketing."[36] The same statement probably holds true for Canada. In neither country is AI as centrally organized and regulated as it is, for example, within the CECOS network of centres in France. It is quite true that "the perceived legal difficulties, general desire for secrecy, and cottage-industry nature of AID have all conspired to prevent any meaningful standards from developing, and make any future for AID the product of chance rather than policy."[37] This view does not represent the opinion of only one independent observer. The Curie-Cohen study takes a similar position: "As compared to other medical practices, artificial insemination with donor is highly secretive. . . . Such secrecy can seriously impede a critical examination of artificial insemination and its consequences."[38]

Policies that are not based on adequate data are bound to fall short of social need. Few knowledgeable people would want to see the practice of AI stifled by excessive rules and rendered more difficult for couples who have suffered the emotional crisis of infertility. This is particularly true when considerable effort is being made in North America generally to free citizens from excessive official regulation of their lives. Nevertheless, there are serious problems associated with the use of AID, "and neither professional standards of practice nor the law has kept pace. Even more disconcerting, perhaps, is the absence of reliable data so vital to the process of developing and implementing effective standards and policy."[39]

Health and Safety: The Screening of Donors and Recipients

If AI is to qualify as a medical procedure, the minimizing of injury caused by that procedure must be both a medical and a public issue: "Clearly the most pressing of these concerns is the possible transmission of infectious and genetic diseases from donor to recipient, with debilitating and perhaps fatal consequences for the AID child."[40] The American Medical Association urges the screening of donors according to the possibilities of current knowledge.[41] That knowledge is now rapidly increasing. An awareness of the need for caution in selecting donors is rarely absent. The issue is whether the screening of donors can be standardized in a practicable manner and what the test for the screening process should be. "For public health reasons, the development of uniform and minimum standards of practice oriented to the well-being of the recipient and progeny is essential."[42]

A report published in British Columbia in 1975 recommended that any person "who cannot supply a verifiable family history should be prohibited from being a donor."[43] A detailed medical and genetic history of the donor and his family is perhaps the approach used most frequently to screen donors. Is this approach adequate? If it is the only screening method used, does the screening process correspond to the current state of knowledge and technique?

There are indications that in practice "the donor-related history often falls far short of obtaining the necessary details."[44] The Curie-Cohen study found that

> donors are not a random sampling of the general population but are a select group with presumably above-average health and intelligence. Beyond the use of this select donor pool, there is little further screening. Most respondents took family medical histories (96 per cent), but this questioning was often merely asking a donor if any genetic diseases existed in his family or presenting him with a short checklist of common familial diseases. A number of doctors expected medical students and hospital residents to screen themselves before donating semen.[45]

Moreover, limiting the screening process to donor-related medical and family histories does not seem to correspond to the current state of knowledge and technique. Prenatal diagnosis, in use since the late 1960s, is increasingly practised in Western societies. Chromosomal and biochemical analyses are available to detect a range of anomalies that would or could produce a defective child. Should these tests be made a standard part of the donor-screening process?

In 1979 the American Association of Tissue Banks approved a set of provisional standards for the freezing and storing of human sperm. These standards state that the "ideal basis for proper donor selection requires personal, physical and genetic examination and history of individuals, as well as an in-depth semen analysis which includes microbial screening."[46] Should this ideal be adopted as the basis for public policy on donor screening?

The Curie-Cohen study found that very little genetic screening and biochemical testing of donors was actually performed. Moreover, to a great extent, the screening that did occur "was performed by physicians who were not trained for this task."[47] The study identifies a target for a public policy on donor selection for AI:

> The screening of donors for genetic diseases is inadequate. A list of genetic traits needs to be established that can be used routinely for screening donors. This procedure will ensure that children born through artificial insemination have a minimum number of genetic defects. This screening should be conducted by people trained in recognizing and evaluating genetic traits.[48]

Everyone agrees that some genetic screening of both donors and recipients is a medical responsibility today. It is a fact that the complexity, difficulties, and expense of donor insemination will rise in proportion to the number and variety of tests that are required. It is generally agreed that screening tests should not be required simply because they are available. Few experienced people in the field would ask that donor and recipient screening use *all* the available chromosomal and biochemical tests. An absolute requirement of this sort would make donor insemination practically impossible.

One might propose as a general rule that the number and variety of tests required, as well as their cost, "must ultimately be balanced against the degree of genetic risk and the benefits of screening."[49] The authors of this general rule, in an article dealing with a recessively inherited enzyme deficiency resulting from AID, recommended possible additional measures for donor and recipient screening.[50] Table 1-1 presents the authors' recommendations.

The Advisory Committee report suggests that "the minimum standard to reduce the risk of genetic disease should be the completion of detailed genetic inquiry."[51] The report specifies the genetic criteria that a donor must meet, but does not specifically mention that the recipient meet the same criteria. These criteria are as follows:

TABLE 1-1
Suggested Measures for Evaluation of Disease Risks in Participants in Artificial Insemination

Recommended measures

- Patient survey for genetic risk factors (D,R)[a]
  - Advanced maternal age
  - Congenital deformity
  - Drug use
  - Teratogen exposure
  - X-ray exposure
  - Venereal disease
- Family survey for genetic diseases (D,R)
  - Rh-incompatibility testing (D,R)
  - Sperm count and morphology studies (D)
  - Carrier testing of members of populations at high risk for testable traits (D,R)
  - Tay-Sachs disease
  - Sickle-cell anemia
  - Thalassemia
  - Informing participants of genetic risks (D,R)

Additional measures of possible value

- Detailed pedigree (D,R)
- Formal genetic counselling (R)
- Banded chromosome study (D,R)
- Carrier testing of all participants for testable traits (D,R)
- Tay-Sachs disease
- Sickle-cell anemia
- Thalassemia

Source: William G. Johnson, Robin C. Schwartz, and Abe M. Chutorian, "Artificial Insemination by Donors: The Need for Genetic Screening," *New England Journal of Medicine* 304 (1981), p. 756. Reprinted by permission of the *New England Journal of Medicine*.

[a] "D" denotes sperm donor and "R" recipient.

Genetic Criteria

1. The donor should be healthy. In particular he should not have, or have had:
    1.1 Any non-trivial malformation such as: cleft lip, cleft palate, meningomyelocele, congenital heart defect, congenital hip dislocation, congenital club foot, hypospadias.
    1.2 Any familial disease with a major genetic component in the etiology such as: asthma, diabetes mellitus, psychosis, epileptic disorder, hypertension, rheumatoid arthritis, severe refractive disorder.
    1.3 Any non-trivial Mendelian disorder such as: albinism, hemophilia, hemoglobin disorder, neurofibromatosis, tuberous sclerosis, hereditary hypercholesterolemia.
2. The donor should not be heterozygous for any recessively inherited gene known to be prevalent in the donor's racial group and for which heterozygosity can be detected such as: thalassemia and G6PD deficiency in Mediterranean races, sickle-cell disease in blacks, Tay-Sachs disease in Ashkenazi Jews and French Canadians.
3. The donor's first degree relatives (parents, sibs, children) should be free of:
    3.1 The conditions referred to in 1.1.
    3.2 Major psychoses, epileptic disorders, juvenile diabetes mellitus, early onset coronary disease (hereditary hypercholesterolemia).
    3.3 Non-trivial disorders showing Mendelian inheritance in the following categories:
        3.3.1 Autosomal dominant or X-linked inheritance with age of onset distribution that extends beyond the donor's age, such as Huntington disease, Landouzy-Dejerine muscular dystrophy, retinitis pigmentosa.
        3.3.2 Autosomal dominant inheritance with reduced penetrance, such as: Marfan syndrome, retinoblastoma, Alport disease.
        3.3.3 Autosomal recessive inheritance with a high frequency in the population such as: cystic fibrosis of the pancreas in Caucasians.

3.3.4 A chromosomal rearrangement or unbalance if other than a proven trisomy, unless the donor is found to have a normal karyotype.[52]

The Advisory Committee report states that "the percentage of AID babies with known congenital defects is less than is expected after natural conception."[53] This claim might encourage the view that it is consequently unnecessary and possibly unfair to demand greater certainty against genetic risk when AI is performed than when babies are conceived by sexual intercourse. Others may take the view, however, that AI is still largely a medical procedure, and it may be reasonable to set more stringent conditions for a medical procedure than would be practical or possible for natural conception.

Record Keeping

The keeping of accurate records is an integral part of medical practice. What is standard procedure in other areas of medicine, however, is viewed as particularly threatening by some practitioners of AI. The potential value conflicts are real, particularly in a society that has not yet devised adequate legal protection for child, donor, recipient couple, and practitioner.

The existence of records linking donors to children born from AI is seen as a threat to the anonymity that nearly everyone believes should be maintained. The value at stake is privacy: that of the donor, the child, and the recipient couple. The maintenance of privacy is linked to the protection of the emotional tranquillity needed for balanced development. Perturbations of the deep and strong emotions and attachments surrounding the event of human reproduction can have destructive results on everyone involved.

The availability of linked records is, however, essential to the proper exercise of medical responsibility, particularly the responsibility that arises with increasing knowledge about transmissible infections and heritable diseases. Such records are necessary to identify, inform, and discontinue the use of dangerous donors. Records are also required to control the frequency with which an individual donor is used. This is particularly important in areas with a small population.

Some argue strongly that linked records are necessary if an AID child is ever to have the possibility, whatever the need may be, of identifying his or her biological father. Attitudes have evolved in Western society about adopted children and the painful search of many to find their biological parents. It is generally recognized that adopted children need to be protected against the potentially devastating effect of discovering parental deception. This protection of adopted children increasingly takes the form of sensitive early disclosure. Canadians live in a quite open, rapidly evolving society. Attitudes about AI may well change also. In such a context, the criticism George Annas has directed against the non-availability of linked records merits consideration:

> Since we do not know what the consequences of this will be, it cannot be said that destroying this information is in the best interests of the child. The most that can be said for such a policy is that it is in the best interests of the donor. But this is simply not good enough. The donor has a choice in the matter, the child has none. The donor and physician can take steps to guard their own interests, the child cannot.[54]

In the social context of contemporary Canada, it would seem that protecting anonymity is viewed as more important than assuring AI children easy access to their biological fathers. A significant change in attitudes may, however, necessitate a change in practice in this matter. The report of the Swedish Insemination Committee, after lengthy consideration of arguments for and against meausres that would give a child information about an AID father, concluded: "Due regard to the AID children requires that these children – like all other children – have in principle the right to be informed at adult age of the identity of the natural father."[55]

A final point should be considered. The frequently mentioned need for more adequate studies on the psycho-social consequences of AID has already been mentioned. Such research would be extremely difficult without adequate records properly stored for a sufficient time. One may also question whether AID children and families ought to be particularly selected as targets for follow-up studies. Are they really so much more in need of study than the children and families who have employed natural insemination?

The Advisory Committee report admits "that the benefits of the maintenance of records which can be linked outweigh the disadvantages. The committee would therefore like to recommend that linkable records be kept in AID. However, at present this recommendation cannot stand until several important legal steps have been taken."[56] The report recommends the enactment of provincial legislation to ensure:

1) That no legal relationship exists between the donor and the child fathered by his sperm.
2) That the donor has no legal responsibility to anyone arising from the sperm donation if he has given full and accurate answers, to the best of his knowledge and belief, to the questions asked of him by the physician involved, concerning his genetic background and medical history.
3) That the standard of care required by the physician is that of reasonable care and that the physician has no legal responsibility to the child beyond exercising that reasonable care in the obtaining of sperm and the insemination.[57]

Legal Status of the AID Child

If "a community prepared to tolerate AID has a duty to protect the interests of the resultant children," what should be the legal status of a child conceived by AID?[58]

In England in 1960, the Departmental Committee of Human Artificial Insemination (the Feversham Committee) recommended in its report that "there should be no amendment of the laws relating to the legitimacy or registration of birth."[59] Opposing this view in a memorandum of dissent, two members of the committee recommended that "i) the definition of legitimacy should be extended to include a child born as a result of AID to which the husband of the mother has consented; and ii) for the purposes of registration of birth of such a child the husband should be deemed to be the father of the child."[60]

In 1961, Robert Pollard made the following comment on the Feversham Committee's recommendation:

> The simple question is—is a child conceived by AID with consent, in effect a member of the family of the father and mother?—and there can be only one answer to this. It is as much a member of the family as a child which is legally adopted into the family. . . . If the Committee had really put the interests of children first then it is inconceivable that they could have come to this contrary conclusion.[61]

In 1973, the Panel of Human Artificial Insemination, appointed by the Board of Science and Education of the British Medical Association, issued a report that referred both to the Feversham Committee's recommendation and to the counter-recommendations of the two dissenting members. The panel's report stated that little had changed legally since the 1960 Feversham report: "As the law stands at present, a child born as the result of AID is illegitimate and the husband's consent to the artificial insemination is immaterial."[62] The panel noted a change in public attitudes toward AID since the time of the Feversham report and a trend in judicial thinking that "would presume that a child was legitimate until evidence was produced to the contrary. That is, if a child is living in an ordinary household where there are a husband and wife who could be presumed to be his parents."[63] The panel joins this trend and proceeds a step further with its strong approval of the dissenting recommendation that the notion of legitimacy should extend to the child conceived by AID with the husband's consent.

This debate in England contains the essential elements of the issue of legitimacy of the AID child. The status of the AID child varies from country to country. Three nations of Europe, the Netherlands, Switzerland, and Portugal, have statutes protecting the legitimacy of the AID child.[64] Under present law in France, paternity may be attributed to the donor if his identity is discovered, and "the husband retains sole control of the consequences of his consent to AID."[65] This means that a husband's petition to disown an AID child "could inevitably be granted, whatever the previous intent of the husband, despite the fact that he had granted his assent to the procedure."[66]

In Canada, generally, it appears that the AID child is illegitimate. Bernard Dickens, a law professor at the University of Toronto, observes:

> This is so even when a husband gives consent to the procedure, on analogy with the illegitimate status of a condoned adultery. In *People* v. *Sorenson*, the Supreme Court of California held a consenting husband to be the lawful father for maintenance purposes, but even if this view commends itself in principle to Canadian courts, which is not certain, the same may not be held for other purposes, such as succession.[67]

Quebec law, in the view of one commentator, is much more protective of an AID child's legitimacy:

> Il favorise sa légitimité souvent au dépens même de la vérité estimant que la première représente une valeur plus fondamentale que la seconde en raison des conséquences pécuniaires favorables entraînées par le statut d'enfant légitime. . . . En pratique donc, . . . il est

> difficule, sinon impossible de contester la légitimité d'un enfant né pendant le mariage d'une hétéroinsémination.[68]

Though several other legal aspects of AID merit mention, this question of the status of the AID child, still doubtful in many parts of Canada and the world, seems to be a matter particularly in need of public policy regulation. The Advisory Committee report recommends that "there should be provincial legislation to ensure that a child born by AID is recognized as a legitimate child of the mother and her consenting husband."[69]

Cryobanking Human Sperm

Since the work of J.K. Sherman, R.G. Bunge, and W.C. Kettel during the years 1953-1955, human sperm has been frozen, stored, thawed, and successfully used to induce pregnancy in women and to produce normal children.[70] At the Paris International Symposium in 1979, Sherman reported that "an estimate in 1978 of over 3,000 births from the clinical use of frozen stored human semen was considered conservative. Currently, the figure is over 5,000."[71] Though exact counts of the number of commercial and noncommercial human sperm banks vary, it seems quite certain that, as of 1979, France had 15 national sperm banks as part of the CECOS network. In the United States 13 non-commercial sperm banks, as well as at least 4 commercial ones with at least 8 branch offices, had been established as of 1979. In Canada, where sperm banks are noncommercial, 3 of 11 clinics use frozen sperm.

Sperm banks have had an uneven history in North America. Among the factors that limited the expansion of sperm banking in the early 1970s, particularly the development of commercial sperm banking, was low professional and public demand. Many practitioners, perhaps because of the lower fertilizing capability of frozen and thawed sperm, have preferred to use fresh sperm. Moreover, the expectation in the early 1970s "that millions of men would elect to store their semen as so called 'fertility insurance' prior to undergoing vasectomy" did not materialize.[72] Why? One writer surmises:

> Those who opted for sterilization had little interest in taking out 'fertility insurance' on their sperm. Where semen storage was offered free prior to vasectomy, less than one percent of patients were interested in it. The 1972 reports, discouraging the public from using

> semen banks in cases of oligospermia, dampered any demand that might have been forthcoming.[73]

Motivations unrelated to vasectomy may ensure the "unspectacular but progressive" development that Sherman foresees for human semen cryobanking in the coming years. He predicts "that there will be a more intense interest in cryobanking for AIH, primarily in pre-therapy storage and in-job related pre-exposure storage as protection against both deliberate and accidental exposure to environmental agents which may compromise fertility or, even worse, compromise development of normal progeny."[74]

Whatever the future of cryobanking may be, "the social and public policy issues that were of concern in the early 1970s remain relevant. Irrespective of the current state of the industry, it is imperative that society examine the implications of the application of semen-bank technology."[75] This opinion, expressed in 1976, still holds true.

Advantages and current limitations. The question of the efficacy of frozen and thawed human sperm, though primarily scientific and medical, has public policy implications. Necessary therapeutic interventions, such as surgery, irradiation, or chemotherapy—as well as work-related exposure to sperm-damaging environmental agents—can cause a permanent deprivation of the capacity to produce sperm or sperm capable of fertilization. Many persons threatened with irreversible infertility may well consider the ability to father children in the future to be an inestimable advantage offered them by the current technology for freezing, storing, and thawing sperm. The reality of this advantage may be restricted, however, by the limitations of current cryotechnology.

What are some of these limitations? First, though estimates vary, experts generally agree that frozen sperm is significantly less successful in fertilizing ova then fresh sperm. Because freezing without a protective agent kills spermatozoa, the two methods of freezing human sperm generally in use today each use a different protective agent. The Sherman method mixes semen and glycerol in a proportion of 10 to 1, and the sperm is frozen in vapours of liquid nitrogen and stored in liquid nitrogen at -196.5°C. The Behram-Sawada method mixes semen with a glycerol-egg yolk-citrate buffer in 1 to 1 proportion. Though both methods produce thawed sperm that are capable of fertilizing, a decrease in spermatozoa motility remains "the most striking effect of semen freezing."[76] The ideal protective agent has yet to be found. As one recent study concludes, "it is evident that the methods of cryoprotection presently available are of limited efficacy and, thus, research must continue in this area."[77]

Second, the fertilizing capability of frozen/thawed human sperm varies from donor to donor. It may also vary with storage time and general physiological condition for any one donor. According to one estimate, semen specimens with initial sperm counts of between 40 million and 200 million per millilitre and motility measures of between 60 and 80 per cent hold the best promise of withstanding long-term storage.

Third, the effects of long-term storage on the fertilizing capability of human sperm are still uncertain. Though Sherman has reported three pregnancies resulting in one miscarriage and two normal births from the use of semen that had been freeze-stored for 10 years, these results are rare. Physicians generally try to use frozen sperm within six months of freezing. One study concludes "that the fertilizing capacity of cryopreserved semen is maintained for at least 5 years."[78] The same study warns that the principal objective of cryopreservation, the semen's ability to initiate a pregnancy, "has never been systematically studied."[79]

Another study reports on nine cases of couples returning for AIH with the use of pre-therapy frozen sperm that had been stored for periods ranging from six months to three years. No pregnancies resulted. This study concludes:

> The results of long-term storage were unpredictable. Some specimens maintained good motility, most others did not, although initial motilities were comparable. The motility of specimens from the same donor showed significant variations. Because of this unpredictability, it is important not to oversell the concept of "vasectomy insurance" as is being done by some commercial semen banks in the United States. When semen is being deposited, one must emphasize that long-term storage is not a guarantee that fertility can be preserved with current technology.[80]

Exploitation of uninformed expectations. The conclusion quoted above has identified the issue of potential witting or unwitting exploitation. Typical victims of imprudent expectations about sperm banking might be a young married couple, the husband of which has to undergo potentially life-saving therapy with permanent infertility as a side-effect. "It is too easy to exploit, even unintentionally, the desperation of such a couple, and it would be cruel and unethical to engender false expectations."[81]

The ethical issue translates into a public policy issue on the regulation of advertising and the standards of informed consent that sperm banks should follow.

Public accountability of sperm cryobanks. A system of certification or accreditation of sperm cryobanks merits serious consideration, though this study is not the place to outline such a protocol. The question of uniform standards is at issue, which includes the practice of importing sperm from countries or regions that apply quite different standards to the collection, preservation, processing, and use of human sperm.

Standards for the selection and screening of donors were addressed in a preceding section. The standards of informed consent that cryobanks should follow is also an issue. Mark Frankel has recommended the following:

> As a minimum requirement, informed consent in human-semen banking should include:
> (1) An understanding by donors and recipients that there is no "guarantee" that frozen semen will be usable at a later date, or that pregnancy will result;
> (2) A recognition of the possibility of adverse medical or genetic consequences;
> (3) An agreement that the recipient and her husband will not seek to identify the donor, and that the donor and his wife will not seek to identify the recipient;
> (4) A statement of the donor's willingness to undergo thorough questioning as to medical and genetic history and subsequent tests;
> (5) An understanding on the part of the donor's wife that her husband's semen will be used for artificial insemination, with the result that he may father a child of which she is not the mother; and
> (6) Current information about the technology of human-semen cryobanking.[82]

The standards of informed consent should also require that cryobanks clearly inform those involved of any potential uses that might be made of frozen sperm for research; for example, for in vitro fertilization.

Standards, though necessary, may not of themselves be sufficient to protect the public from those who would look upon sperm banking as just another potentially profitable business venture. J.K. Sherman, a leader in the cryobanking of sperm, has warned: "'Fly-by-night' unscientific and irresponsible commercial enterprises may not employ care in genetic selection of donors, screening of semen, testing for venereal disease, and the like."[83] Recent references to the coming availability of home, "do-it-yourself" artificial insemination kits might give added support to the plea for caution.

Particular applications of frozen semen: sex selection, eugenics, post-mortem insemination. The use of frozen sperm could extend or facilitate the use of artificial insemination, by the husband or by a donor, for the purposes of selecting the sex of children before conception. Because this practice could affect the population's sex ratio, family size, and birth-order patterns, these potential social consequences have been the subject of debate for at least 15 years. The discussion has necessarily been quite speculative.

Mention is occasionally made of sporadic attempts to use AI selectively with eugenic motivation, as in a reported attempt to inseminate intelligent, beautiful women with the sperm of several Nobel Prize-winning scientists.[84] With the exception of such occasional, rather bizarre, and generally genetically uninformed endeavours, there is little evidence of any serious program to use artificial insemination and frozen sperm to obtain the eugenic goal of improving the genetic quality of the human species.

There have been reports of a husband's frozen sperm being used after his death for artificial insemination of his surviving spouse. The best interests of the child is the primary focus of the several issues raised by this practice. Yet the interests of public order also have to be considered. Posthumous fertilization leading to the fathering of children long after the father's death could disrupt the order of inheritance and succession. With this problem in view the Warnock report recommended "that legislation be introduced to provide that any child born by AIH who was not *in utero* at the date of the death of its father shall be disregarded for the purposes of succession to and inheritance from the latter."[85] Post-mortem insemination obviously sets up a tension between the good of the child and the good of public order.

Criteria of exclusion. Practitioners sometimes do not know on what basis they could or should refuse requests for AI. Should they refuse the request of a single woman who has no intention of living with the man who would be the father of the child? Should they refuse the requests of lesbian couples? In other circumstances serious doubt exists about a couple's ability to parent a child properly or about a woman's ability to carry a child without causing fetal damage.

Criteria are sorely needed to support the exclusion of certain people, as well as to avoid bias and arbitrariness in the refusal of requests. The Advisory Committee to the Canadian Minister of National Health and Welfare offers a basis for the establishment of criteria of exclusion: "That while AID is a benefit conferred by the progress of medical science, the bearing of a child by AID is neither a right which should be claimed by anyone nor an obligation which should be imposed upon anyone."[86]

In Vitro Fertilization and Embryo Transfer

A Synopsis

Procedures now exist that permit the harvesting of human ova at the proper stage of development for fertilization, the actual fertilization of these harvested ova in the laboratory, the sustenance of the resulting embryo for a period of time in the laboratory, and the transfer of that embryo to the uterus, with successful implantation and normal fetal development up to birth. "In vitro fertilization" and "embryo transfer" are terms generally used to cover these new techniques in human reproductive technologies.

The first well-documented achievement of human IVF appeared in 1970 in a report by R.G. Edwards, P.C. Steptoe, and J.M. Purdy.[87] Many successful occurrences of laboratory fertilization of human ova by human sperm have been achieved in the ensuing years. Attempts to transfer the human embryo resulting from IVF were reported in the early 1970s, and several successful implantations were achieved. It was not until July 25, 1978, however, that a pregnancy achieved by IVF and embryo transfer resulted in a live, normal birth. On that date, Louise Joy Brown was born to Mr. and Mrs. Gilbert John Brown in Oldham General Hospital near Manchester, England. Many other pregnancies and normal births have been achieved since the birth of Louise Brown.

Centres in England, Australia, United States, Canada, and other parts of the world now actively practise and seek to perfect the techniques of IVF and embryo transfer. This aspect of human reproductive technology has generated many professional publications on the scientific, medical, and ethical questions as well as thorough inquiries and reports on public policy issues by government-appointed committees in several countries.

It is important to note that the procedures under discussion are not "an isolated trick ingeniously conceived by two men to meet an individual problem."[88] Many years of experience with IVF and embryo transfer in animals, as well as years of painstaking work on the complexities of the human reproductive system, preceded and made possible the successful human application of these techniques.

The laboratory fertilization of human ova need not be, and frequently has not been, followed by embryo transfer. The ability to preserve human embryos in the laboratory for a period of time after fertilization suggests the possibility of undertaking research on the human embryo. Clinical and research applications raise distinct sets of issues.

The Procedures

It is unnecessary for the purposes of this book to offer a complete and detailed description of each step in the laboratory fertilization of human ova and embryo transfer. The present state of the art, preceded by an extensive period of trial and error, is still rapidly evolving. Differences of procedure and controversies on technical matters may be observed among the many groups working on IVF. This chapter will address only those differences and controversies that have public policy implications.

The process of IVF is conceptually simple but technically much more difficult than generally imagined. The laboratory procedure requires mature eggs ready for fertilization, active sperm, a proper medium to combine eggs and sperm, a proper medium to support embryo development, and proper timing for each step of the process. Competent handling of these procedures calls for a team including persons skilled in reproductive endocrinology, sperm and egg collection, fertilization and early cleavage, gynecological laparoscopy, and human infertility.

Step 1. Proper timing of ovum recovery is one of the critical challenges for the success of IVF and embryo transfer. Ova have to be removed from the ovaries at a precise moment in the course of their development if laboratory fertilization is to succeed. Obtaining ova – they are called oocytes at this stage – at this precise moment, and not earlier or later, demands that the menstrual cycle be closely monitored or controlled.

In earlier attempts, women were treated with special hormones, particularly with human menopausal gonadotropin (HMG) and human chorionic gonadotropin (HCG), to stimulate ovulation "and to avoid the difficulties in identifying the time of ovulation during the natural cycle."[89] One medical group abandoned this treament and turned to precise methods to monitor the menstrual cycle because "there were too many difficulties in establishing the correct endocrine situation to sustain pregnancy after the use of HMG and HCG."[90]

The cumulative experience of the past few years now, however, seems to favour some combination of the substances clomiphene citrate CC and HMG or CC and HCG to stimulate the ovaries and increase the yield of ova for fertilization. Alan O. Trounson and John F. Leeton of Australia believe "that clomiphene stimulation of ovarian response and HCG to control the time of ovulation is an extremely useful procedure for in-vitro fertilisation of human eggs and may be used to establish the technique as a routine clinical procedure."[91]

Step 2. The ova, or oocytes, are removed from the ovaries shortly before ovulation. The technique is called "laparoscopy", in which tiny telescope and a fiber-optical illuminator are introduced through a very small incision in the region of the navel; the ovary and any mature follicles can be examined and eggs can be removed by aspiration from the follicles."[92] Follicles are collections of cells that enclose the maturing eggs, or oocytes, before ovulation and are "clearly detectable on the surface of the ovary as thin-walled pink swellings."[93] In the absence of complicating conditions, the pre-ovulatory oocytes may be obtained by a suction technique utilizing an aspiration needle fitted inside a medium-bore needle sleeve. If all goes well, the phase of the procedure from laparoscopic visualization of the follicle to placing the oocyte in a sperm suspension for fertilization is quite rapid, ranging from 85 seconds to 20 minutes.

Step 3. After aspiration, the oocytes are placed in a special medium under a specific pressure and a free flow of gas consisting of 5 per cent oxygen, 5 per cent carbon dioxide, and 90 per cent nitrogen. After they are examined to ensure activity and absence of pathogenic organisms, the spermatozoa to be used for fertilization are subjected to gentle centrifugation to remove seminal plasma. The oocytes are then transferred to suspensions of spermatozoa in a concentration of 10.6 per millilitre. This detail is important to the possible use of IVF for couples when the husband or male partner suffers from oligospermia, that is, when there are too few sperm per ejaculate to achieve fertilization. Fertilization normally occurs a few hours after sperm and ova are combined. The precise criteria employed to determine that fertilization has occurred, as well as the possiblity of states that imitate fertilization, are still the subject of scientific discussion.

Step 4. The fertilized eggs are placed in a special medium supplemented with human serum, approximately 18 hours after insemination. An embryo, a fetus, and eventually a normal baby will result from these procedures cnly if the initial 46-chromosome cell resulting from fertilization divides properly. This process is called "cleavage." Earlier studies showed that "the first cleavage occurred betwen 18 and 39 hours after insemination, although these times are approximate. The second and third cleavages occurred between 38 and 46 hours and between 51 and 62 hours respectively."[94] This cleavage timing has also characterized the development of fertilized eggs in more recent attempts to achieve successful IVF.

Step 5. The embryo resulting from IVF may be placed in the uterus via the cervix without anaesthesia, or surgically, with placement following a laparotomy (surgical incision of the abdominal wall). Timing and matching the developing embryo to the state of the uterus is essential if implantation and pregnancy are to occur. Successful implantation also depends on the stage of growth, that is, on the number of cell divisions attained by the embryo at the time of transfer. Embryos are usually introduced into the uterus when they are at the four-to eight-cell stage. The usual practice is to transfer more than one embryo at the same time. This practice increases both the chances of achieving a pregnancy and of achieving multiple pregnancies resulting in the bith of twins or triplets.

State of the Art: Divergence, Uncertainty, and Unknowns

Uncertainties and unknowns as well as differences of practice, procedure, or technique among the many groups now using IVF and embryo transfer to treat infertility mark nearly every step of the process.

Patient selection. Choosing patients for IVF and embryo transfer would seem, at first sight, to be relatively straightforward and uncontroversial. These new reproductive techniques have been developed as a treatment for infertility and are most promising when a couple's infertility arises from defects in the woman's Fallopian tubes. Blockage of these tubes can have many causes. Moreover, surgical removal of the tubes may have been necessary because of a previous ectopic pregnancy (location of the fertilized ovum outside the uterus, as in the Fallopian tubes) or cancer. A couple's infertility may also be due to oligospermia. In either of these situations IVF and embryo transfer may help a couple have their own child. These procedures may also lead to the birth of a child when the woman carries antibodies against spermatozoa, has a cervical mucus hostile to sperm, when both partners are affected by conditions that compound their infertility, or when the couple suffers from idiopathic, or unexplained, infertility.[95]

Even with these classic cases of infertility, for which IVF and embryo transfer appear to be a promising treatment, clinics may differ on the age limit they set for acceptable candidates. Some clinics may not accept women over 40 years of age on the grounds that the rates of pregnancy failure and of fetal chromosomal defects rise with advanced maternal age. Clinics may also differ on the advisability of using IVF and embryo transfer in combination with ovum donation, embryo donation, or surrogate motherhood, as will be discussed in a following section of this chapter. Occasions to use these procedures could well arise when women suffer from ovarian or uterine defects that prevent them either from producing fertilizable eggs or from carrying a child.

The use of social, psychological, or genetic criteria to control access to IVF services may reveal even wider divergence of policy among clinics. Some persons, for example, may think it advisable to limit these services to married couples or to heterosexual couples living together in a stable relationship. Others may view such restrictions as discriminatory and unjustifiable before the Charter of Rights and Freedoms.

Stimulation of the ovulatory cycle. This procedure, by use of clomiphene citrate, human menopausal gonadotropin, human chorionic gonadotropin, or some combination of these has become a regular part of IVF treatment of infertility. These substances lead to the production of larger numbers of eggs ripe for fertilization and help physicians gauge the time of ovulation and the opportune moment for laparoscopic retrieval of ova. Scientists are uncertain about how these various stimulation protocols affect fertilization, cleavage, and the pregnancy success rate. The group or cohort of follicles obtained after stimulation of the ovulatory cycle may not equally exhibit the stage of development required for successful fertilization. One expert in this field, Alexander Lopata, has stated:

> The challenge for the future is to devise a procedure that can identify follicles of different quality within the cohort. An even more useful breakthrough, however, would be to develop an ovarian stimulation program that optimizes the synchrony between follicles in the developing cohort.[96]

Opinions differ on whether superovulation treatments—stimulation of the ovulatory cycle—damage the ovaries and, if so, on what the precise mechanisms of such damage really are. Lars Hamberger, from Sweden, has stated, "We believe that heavy super-ovulation damages the ovaries in many of our patients, and we prefer to avoid excessive stimulation."[97] Dr. Hamberger mentions cases of women having no remaining follicles and entering premature menopause after such treatments. He has suggested that repeated superovulatory treatments may disturb the ovary's microcirculatory processes and lead to destruction of adjacent follicles. Dr. Alan O. Trounson has said, however, that there is no physiological basis for such conclusions. Dr. Georgeanna S. Jones, from Norfolk, Virginia, doubts that HCG could cause the follicular damage noted by Dr. Hamberger. Dr. Robert G. Edwards, from Bourne Hall, England, questions whether high levels of progesterone or the formation of corpora lutea (the yellow substances formed in the ovary where the follicle ruptures) could, as Dr. Hamberger claims, disrupt the process of follicle growth. Dr. Edwards has added, "There can be so many other explanations: perhaps the exogenous gonadotropins have induced a Stein-Leventhal syndrome, producing a series of cystic follicles. I find it difficult to evaluate his [Hamberger's] results on the basis of the present evidence."[98]

Multiple embryo transfer. There is disagreement about the number of embryos that should be transferred to the uterus after IVF. Many practitioners have noted that multiple embryo transfer increases the probability of a successful pregnancy. In one study, John F. Kerin and others observed an increase in the overall pregnancy rate from 31 per cent to 39 per cent to 50 per cent, respectively, as two, three, and four embryos were transferred.[99] In another study comparing different IVF treatment protocols for the years 1980, 1981, and 1982, Alexander Lopata concluded, "By far the clearest outcome of the 1982 study was the highly significant increase in the pregnancy success rate with the increasing number of embryos transferred to the uterus."[100]

Multiple embryo transfers also increase the chances of multiple pregnancies and twin, triplet, or quadruplet births. Alexander Lopata refers to one series of patients receiving IVF treatment in which multiple embryo transfer increased the twinning rate by 30 times compared with the twinning rate of the general population. The incidence of triplets following transfer of three or four embryos could prove to be 40 to 100 times greater than in the general population. Whether multiple embryo transfer increases the probability of ectopic pregnancy is currently unknown.[101]

Though couples suffering from infertility may desire a child intensely, some may find twins or triplets to be an undesirable burden. Moreover, multiple pregnancies carry an increased risk of mortality and congenital malformations. This increase holds for twins as compared with single pregnancies and is even greater for triplets and higher multiple pregnancies.

John Kerin and others have warned that "in-vitro fertilisation and embryo transfer programmes may face high multiple-pregnancy rates as the quality and number of embryos available for transfer rises."[102] They recommend restricting the number of transferred embryos to limit multiple pregnancies to twins and suggest that, with improvements in procedure, "it may become possible to maximise pregnancy rates with the transfer of 1 embryo for a singleton pregnancy or to minimise the risks of multiple pregnancy by limiting transfers to 2 embryos."[103] Other practitioners are wary of hard and fast rules governing multiple embryo transfer while the IVF and embryo transfer process is undergoing rapid evolution. Some would also conclude that the benefits of successful pregnancy would now outweigh the risks of multiple pregnancy. Judgments differ.

Cryopreservation of human embryos. The frozen storage of human embryos and the transfer of thawed human embryos after IVF, thought by some practitioners in 1981 to be possible only in the distant future, may soon be used more frequently. Alan O. Trounson and Linda Mohr reported in 1983 that a pregnancy was achieved after thawing and transfer of an embryo that had been frozen at the eight-cell stage and preserved in liquid nitrogen for four months. The termination of the pregnancy at 24 weeks gestation and the death of the female fetus were due to infections. Trounson and Mohr report that there appeared to be "no abnormality of the fetus at week 24 which could be associated with cryopreservation of the embryo."[104]

A clinical rationale supports the use of frozen and thawed human embryos in IVF and embryo transfer. Trounson and Mohr have summarized part of this rationale: "Preservation of embryos for a limited time allows fewer embryos to be replaced on several different occasions and thus the problems of multiple pregnancy can be minimized, the effectiveness of a single IVF procedure increased and embryo replacement in adverse maternal conditions avoided."[105] Stored embryos could spare an infertile woman the risks of additional laparoscopies to obtain ova for renewed attempts to achieve pregnancy after initial tries failed.

Few clinics have to date reported attempts to transfer frozen and thawed human embryos after IVF. Though quite extensive experience with freezing and thawing various mammalian embryos seems to indicate that pre-implantation embryos can weather damage by cryopreservation to several of their cells, or blastomeres, the story may be quite different for the human embryo. Researchers simply do not yet know. There is hardly any way to resolve such doubts or perfect the cryopreservation techniques, if necessary, without experimenting with the human embryo. Most people would agree that decisions about allowing experimentation with the human embryo, or about the conditions of its acceptability, should not be made by the scientific community alone.

Ovum and embryo donations. Certain types of infertility may occasion proposals to use ovum donations or embryo donations, with or without surrogate motherhood, in connection with IVF.

A woman who wants to have a child may be unable to deliver a fertilizable ovum, either because of inaccessible ovaries or because of deficient ovum production. She may also refuse to produce a child from her ova because she is the bearer of genes for an inheritable disease. The use of ovum donation, IVF of the donated ovum by her partner's sperm, and subsequent transfer of the embryo to her uterus might be proposed in these situations.

It may also happen that a woman is unable to carry a child becuase of uterine disorders or some other condition, such as severe recurrent toxemia (toxins in the blood). If she is able to produce adequate ova, IVF of these with her husband's sperm could be followed by transfer of the embryo to the uterus of another woman, who would carry the fetus to term and return the baby to the couple. This arrangement would combine IVF and embryo transfer with surrogate motherhood.

Ovum donation may also be achieved by a process called "nonsurgical ovum transfer." IVF is not used. A donor woman is artificially inseminated with sperm from the husband of an infertile woman. After lavage (washing out) of the donor woman's uterus, the recovered embryo is transferred to the uterus of the infertile woman. Dr. Maria Bustillo, Dr. John E. Buster, and colleagues have reported that they achieved two pregnancies with this method. In a third attempt, the embryo implanted in the uterus of the donor woman aborted spontaneously nine days later. A fourth attempt resulted in an ectopic pregnancy in the donor woman.[106]

Embryo donation could be proposed if both husband and wife are infertile. In this situation a donated ovum would be fertilized by donor sperm. The embryo could be transferred to the uterus of the infertile woman or, if she has uterine problems, into the uterus of another woman for surrogate mothering.

These reproductive arrangements have legal, social, and ethical implications. Societies and various groups within any given society continue to differ on the acceptability of one, several, or all of these reproductive ploys to overcome infertility.

Embryo loss. Embryo loss continues to plague the process of IVF and embryo transfer. The actual fertilization of ova seems to work well enough; however, Robert G. Edwards and others realize that a major difficulty remains concerning "the proportion of embryos which implant, which is still depressingly low in clinics."[107] The failure rate of implantation after IVF is still generally about 80 per cent, though somewhat lower in clinics with more experience.

The failure of human embroys to implant after IVF may be due to a combination of an extensive range of factors. Some IVF embryos may fail to implant or they may abort spontaneously for the same reasons that partially account for the high rates of implantation failure and spontaneous abortion after fertilization by natural sexual intercourse. It is probable that chromosome abnormalities contribute to the noted high failure rate of implantation after embryo transfer. Chromosome abnormalities are implicated in about 50 per cent of spontaneous abortions in clinically recognized human pregnancies. Little information is available, however, on the incidence of chromosome abnormalities in preimplantation embryos, and the "contribution of lethal chromosome anomalies to very early pregnancy loss *in vivo* is unknown."[108]

Could modifications of procedures and techniques used at various steps in the process of IVF and embryo transfer lead to a reduction of the current 80 per cent loss of transferred embryos? This is highly probable. The techniques involved at each step of the process from ovulatory stimulation, through embryo culture, to embryo transfer may actually contribute to the failure of implantation or to spontaneous abortion. No one, for example, is quite sure whether selection of one particular cell stage over another for embryo transfer favours or works against implantation. As Robert Edwards has explained, "Even today, we do not know if replacements at 4 1/2 or 5 days will give better results than at 2-3 days, because most groups replace embryos in early cleavage."[109]

This is only one example of the many factors that could be implicated in the loss of embryos after transfer. These uncertainties point to the need for controlled research. Dr. Edwards, for example, has argued strongly in favour of research on human embryos. He asserts, "The need for research is fundamental to the process of in vitro fertilization.... The clinical application of in vitro fertilization in all its forms demands research on embryos...."[110]

Differences of procedure, technique, and results are a normal feature of the trial and error process marking the clinical introduction of new biomedical technologies. Cumulative experience may be expected to reduce these differences and lead to the adoption of the most successful and beneficial approaches. Some variances, however, center on matters that transcend the boundaries of laboratory technique and clinical procedure. They raise questions of social ethics and public policy. The major questions will be considered later in this chapter.

IVF and Research with the Human Embryo

Many reasons have been given for research on and with human embryos. Research on the early human embryo was impossible when fertilization took place, as it has since the beginning of humanity, within the woman's body. Today, however, IVF may produce more embryos than needed to treat the donors' infertility or may be used to fashion embryos explicitly for research.

The Royal Society has identified three major purposes for research with the human embryo. They are:

- the improvement of IVF as a therapeutic procedure for the overcoming of certain kinds of infertility;
- the extension of the IVF procedure so as to advance understanding of infertility and to tackle the problem of inherited genetic disease;
- the acquisition of basic knowledge of human development and its disorders.[111]

More specifically, scientists might propose research on the human embryo to achieve important clinical and scientific objectives, such as the following:

- to identify the environmental and genetic factors leading to high rates of embryo loss and spontaneous abortions in humans
- to identify the precise conditions of fertilization, embryo culture, and embryo transfer most favourable

to successful implantation, pregnancy, and healthy development of the embryo
- to develop reliable embryo screening tests to prevent the implantation of genetically defective embryos
- to investigate the mechanisms by which chromosomal abnormalities are produced
- to develop efficient techniques for freezing, storing, and thawing human embryos
- to determine the precise causes of infertility
- to develop and test more effective contraceptives
- to elucidate embryonic cell growth and differentiation and the developmental stages of the human embryo
- to study the sites and modes of action of mutant genes that are lethal for the embryo
- to advance knowledge about gene expression and to develop techniques of genetic surgery that would permit the repair of genetic defects before embryo replacement
- to study the relationship between malignancy (cancer) and cell specialization
- to develop techniques to support the partial development of human cells and organs or of the entire embryo outside the woman's body.[112]

The kinds of experimental manipulation involved in research projects could range from simple observation to culture of the embryo including: developing part of the embryo in culture, dividing the embryo, forming hybrids and chimeras by interspecies fertilization or intraspecies fusion of embryos, inserting genes or chromosomes into the embryo, transplanting the cell nucleus, freezing and thawing the embryo, and treating the embryo with various kinds of agents.

The Royal Society makes an important distinction between early extra-embryonic tissues and the definitive embryo in deciding how long human embryos might be maintained in the laboratory for research:

> The first stage in the development of human fertilized egg is concerned almost entirely with the formation of extra-embryonic tissues that initiate and maintain interactions with the mother. . . . It is not until the fourth week, within the tissues constituting the "early embryo", the cells making up the "definitive embryo" (which will eventually become the fetus) begin to be organized and to grow.[113]

Some research objectives might require maintenance and culture only of embryonic stem cell lines, not the normal organization of the definitive embryo. Other projects might require the normally organized and developing definitive embryo. If so, it is difficult to conceive how such projects could continue for an extended period after fertilization, given the primitive state of current support systems for extrauterine embryos.

A key scientific, legal, and moral question is whether the pursuit of these important objectives necessarily requires that human embryos be investigated. The answer is affirmative for many of these objectives. Variation between species is sufficiently great that accurate knowledge of human embryology can come only from research with the human embryo.[114] If the scientific case for research on the human embryo seems strong, is such research justifiable morally and legally? The moral status of the embryo is one of the most controversial issues in society today. Moreover, those who differ on the moral status of the human embryo frequently find themselves united in concern about how far scientists may be prepared to go in manipulating human life at its origins.

Surrogate Motherhood

The term "surrogate mothering" is used for several novel reporductive arrangements. In the typical surrogate motherhood scenario, a woman, married or not, agrees to conceive and bear a child for an infertile couple. The surrogate mother conceives a child by artifical insemination with sperm from the husband of the infertile couple, carries the fetus to term, and, in keeping with the preconception agreement, gives the child over to the infertile couple after birth. The wife of the infertile couple becomes the social mother of the child.

An infertile couple may also acquire a child by transfer of an embryo from the uterus of a woman who had agreed to be artifically inseminated by sperm from the husband of the infertile couple to the healthy uterus of the wife affected by an ovarian disorder that prevents conception. George J. Annas has summarized the five steps of the nonsurgical transfer procedure used in this situation as follows:

1. Synchronization of ovulation times between the embryo donor and the recipient woman;
2. Insemination of the donor woman with sperm from the infertile recipient's husband;
3. Lavage, or washing out, of the donor's uterus about five days following fertilization;

4. Recovery of the embryo from the lavage fluid; and
5. Transfer of the embryo to the recipient's uterus.[115]

A third and quite different approach may be contemplated if a woman can produce fertilizable ova, but is unable to bear a child because of a uterine disorder. One or several of the wife's ova could be fertilized in vitro with her husband's sperm. The resulting embryo would be transferred to the uterus of a woman agreeing to carry the fetus to term and give the baby over to the infertile couple after birth.

These scenarios, only three of many possible reproductive arrangements, implicate at least three persons – two women and one man – in the conception, gestation, birth, and rearing of the child. A child could even have five "parents," for example, in an arrangement utilizing a sperm donor, an ovum donor, in vitro fertilization, a surrogate mother, and an infertile couple as social parents.

One legal commentator, Theresa M. Mady, has observed that "the novelty of the surrogate mother arrangement lies not in the procedure, but rather in the relationship between the parties."[116] We do not yet have a language tailored to cover these novel relationships. The words "mother," "father," and "parent" carry moral, social, and legal implications. They are not exclusively descriptive terms. Novel reproductive schemes that change the meaning of these words may create, at least temporarily, legal uncertainty, social confusion, and moral quandaries.

Traditionally, one woman fulfilled the genetic, gestational, and social roles of motherhood for a given child. It is now possible to separate and distribute these roles to different women. The terms "mother" and "surrogate mother" inadequately cover the possible distributions of these roles.

In the first of the situations mentioned above, the surrogate mother is both the genetic and the gestational mother. The infertile wife, by adoption or by a mode of relationship equivalent to adoption, becomes the social mother. The distribution of motherhood functions is quite different in the second situation. Here the infertile wife is the gestational and social mother, but the inseminated woman is the child's genetic mother. The infertile wife in the third situation is the child's genetic and social mother. The woman receiving the transferred embryo is the gestational mother, who has agreed to give over the child to the infertile couple after birth.

Is it accurate, legally and morally, to call a woman a "surrogate" mother and is it justifiable to treat her as such when she, in fact, is the child's genetic and gestational mother?

There are, of course, differences between a normal mother and a surrogate mother. In surrogate mothering the presumption is that a woman deliberately conceives a child she has no intention of keeping, loving, and raising. Formerly, an "unwanted" pregnancy usually occurred when a woman undeliberately conceived a child she had no intention of keeping, loving, or rearing. But in surrogate mothering, the situation is novel: the pregnancy is not unwanted, for the conception was deliberate, and the infertile couple deeply desires the child. Three people are knowingly and deliberately collaborating in a venture of joint parenthood. The surrogate mother's role is limited in time but is biologically profound. She enters upon a philanthropic pregnancy or a pregnancy for fee to enable an infertile couple to have the child they want to love and raise.

Surrogate motherhood is not simply the reverse of artificial insemination by donor. There are important differences. The donor of sperm in AID, for example, does not want a relationship of fatherhood to the child to be born and remains anonymous, both to the infertile couple and to the child. But the sperm donor in aritifical insemination of the surrogate mother has every intention of acting as the child's social father.

In one important respect, the relationship of the husband of the infertile couple to the surrogate is like the relationship of the anonymous donor to the wife of an infertile couple in the practice of AID. In neither case is the relationship adulterous, as some have suggested, for the relationship does not involve sexual intercourse and the exchange of sexual love outside marriage.

In the practice of AID, the wife of the infertile couple is the genetic, gestational, and social mother to the child. Her husband is generally presumed to be the child's father, though genetically he is not. In the surrogate scheme, the surrogate acts only as genetic and gestational mother. Her husband, if she is married, may be presumed to be the child's father. The husband of the infertile couple in the surrogate scheme may have to prove his paternity should the initial promises on the surrogate arrangment fail to be honoured.

The differences between AID and surrogate mothering may have particular psychological and ethical significance when one considers how the relationships generated by these reproductive arrangements might be vulnerable to various kinds of pressure. In AID, the sperm donor is an unlikely target of commercial pressure. His involvement is too limited, temporally and personally, to motivate the offering of large sums of money for his services. The surrogate mother, quite to the contrary, is more likely to be offered considerable sums of money to conceive and bear a child for someone else. Depending on her personal and socio-economic circumstances, a surrogate could easily be commercially seduced to do for money and for others what normally brings fulfillment only when it is done for love, for oneself, and for one's own family.

In the practice of AID, a considerable corporeal and psychological distance protects the sperm donor from potential emotional involvement with the child for whose conception he is biologically responsible. A single woman about to enter pregnancy for the first time and, indeed, as a surrogate mother may well come to experience new emotions, emotions of attachment to "her" child. She is not protected by corporeal and temporal distance from such potential involvement with the child. She is open to the emotions attendant upon the possible pain of separation if and when she honours the promises of the surrogate arrangement. Should society treat that promise, made before conception, as legally and morally binding?

Public Policy Issues

The function of public policy in highly pluralistic societies is to maintain social order, protect the common good, and create a framework of freedom for the exercise of moral conscience. When a society houses many divergent moral communities, it is unrealistic, and even potentially dangerous, to demand that public policy be used, with qualification or limitation, to prohibit what is immoral and to promote what is moral. How could this be achieved when reasonable people disagree profoundly on what is right and wrong?

Individuals and communities in North American society hold very different fundamental views and are committed to quite different values in matters of human reproduction. One should not expect public policy pronouncements on every moral or professional issue raised by novel reproductive practice. Seriousness of effect on societal order and the common good is the criterion that should govern both the choice of issues requiring public policy consideration and the possible conditions to be imposed on the exercise of moral liberty.

IVF and embryo transfer, research on human embryos, and surrogate mothering raise many scientifc, clinical, legal, and moral questions that are experienced as pressing and crucial in varying degrees by our society's morally divergent and professionally specialized communities. Some of these matters are best left to the forum of moral discourse; others will be resolved on the basis of accumulated scientific knowledge and clinical experience. The following issues are those that require public policy attention today.

Infertility. The causes, incidence, prevention, and treatment of male and female infertility require and deserve the attention of those responsible for the formulation of public policy and the distribution of societal resources. Though the prevention of infertility is increasingly recognized as a public health challenge,[117] the focus in this discussion of the reproductive technologies is on treatment as a target of public policy.

Treatment of infertility has been a focus of controversy for several years. Three related questions define the public policy issue. Does infertility merit treatment? Should public funds be used for the treatment of infertility? Do the various techniques of assisted reproduction (AID, IVF, surrogate motherhood) count as *treatments* of infertility?

The first question is hardly an issue in the mid-1980s. The primacy of the desire to have children and to build a family combined with the acute, prolonged suffering of those unable to do so have affected public consciousness and practice. It is likely that the majority of Canadians would support the conclusion of the Warnock report "that infertility is a condition meriting treatment."[118]

The question of using public funds for the treatment of infertility is more complex and may be answered differently depending on the nature of the proposed treatment and the cause of the infertility. The global question spawns a family of individual issues. Should public funds be used to cover the costs of microsurgical repair of Fallopian tubes or of the vas deferens after voluntary vasectomy or tubal ligation? Should public funds be used to establish and maintain IVF clinics and to cover the costs of individual treatments? A negative answer raises the question whether one can accept that only infertile persons who are sufficiently wealthy will be able to fulfill their desire for a child. An affirmative answer raises the question of the policy required for a just distribution of resources and equitable access to IVF services.

The question of eligibility for infertility treatment raises the controversial issue of the requisites for parenthood in view of the best interests of the child. Which requisites should be considered normative as a basis for criteria of eligibility? Should infertility treatment, whether publicly funded or not, be available only to those who, married or not, are living in a stable heterosexual relationship? Can single persons be barred from infertility treatments such as AID and IVF if provisions are already in place that enable single persons to adopt children? How do the requisites of parenthood relate to the prohibition of discrimination in the Canadian Charter of Rights and Freedoms? Would criteria of exclusion based on the sexual preference and single status of persons be in conflict with the provisions of the Charter?

It is difficult to predict how the interpretation of the Charter on these matters will evolve over the next few years. Criteria of eligibility, whether based on age, social status, or genetic profile, will remain an issue for public policy for some years to come. It is hardly possible now to design a comprehensive set of criteria that would cover fairly the singularities of every possible case, that would enjoy societal consensus, and that would be able to withstand serious and justifiable challenge. It is essential to the morality of an open society, however, that anyone refused treatment for infertility has a right to an honest explanation of the reasons for exclusion.

A just and rational public policy on the treatment of infertility requires precise data on the causes and prevalence of the various kinds of infertility. It would make little sense to promote the treatment of infertility or to adopt a laissez-faire approach to the proliferation of clinics for assisted reproduction while doing little to prevent infertility, when prevention is feasible. Moreover, a policy of public support for infertility treatment and assisted reproduction needs a secure base of precise information if it is to escape the failures of haphazardness, falsely raised hopes among the infertile, and unjust or unenlightened distribution of public resources.

The Ethics Advisory Board of the former Department of Health, Education, and Welfare (DHEW) in the United States raised two important questions in 1979 about IVF as a treatment for infertility: First, how many women who wish to bear children are infertile because of blocked Fallopian tubes? Second, of these infertile women, how many need in vitro fertilization and embryo transfer in the sense that they have no alternative means for producing children of their own?[119] The report acknowledged that precise data on the extent of these needs was not then available. These two questions offer examples of the kinds of precise estimates of need that are also required in Canada.

The clinical and public policy status of IVF and embryo transfer. There is a strong case for the claim that IVF and embryo transfer "have caught the attention of the world and created more interest in the study of human infertility and its therapy than almost any other development in this century."[120] Knowledge acquired from current and new research uses of IVF and embryo transfer is also likely to have a remarkable effect on human reproduction as a whole and on other domains of clinical medicine as well.[121]

These and like claims, the glamour of novelty and intense media interest surrounding IVF, the hopeful demand for IVF services by many who have suffered the disappointments of infertility, and the IVF promise of better things to come only set the stage for public policy questions. These factors, however impressive they may be, are not an adequate basis for public policy recommendations.

John B. McKinlay's tracing of seven stages in the typical career of a medical innovation is a useful framework that suggests the essential public policy questions to be considered in establishing criteria for public support and funding of IVF and embryo transfer services.[122] McKinlay has described how a new diagnostic or therapeutic procedure frequently passes through the initial stages of a promising report in professional journals or the media, professional adoption, public acceptance and third-party endorsement to reach the privileged position of standard procedure without ever being subjected to controlled and rigorous evaluation. Proposals for methodologically rigorous trials of an innovation frequently are put forward only after public funding and the acquired status of "established procedure" have endowed the innovation with an aura of impregnability.

McKinlay's point in tracing this career course of a medical innovation is to show "just how advanced that career usually is before data suitable for the formulation of social policies involving the allocation of public resources make their entrance."[123] Public policy requires a foundation more solid than the fragile evidence that frequently buttresses the pinnacled postion and public endorsement of medical innovations. McKinlay states, "The claims of manufacturers, the opinions of enthusiastic researchers, the well-intentioned adoption by experienced clinicians and educators, as well as public demand, are no substitute for a proper evaluation, and do not provide a rational, scientific basis for policy decisions."[124]

A just distribution of limited resources, the avoidance of waste, the protection from harm and false expectations, and the enhancement of the common good require that public policy on medical innovations be guided by the following criteria. The *nature and magnitude of human needs* for new diagnostic and therapeutic procedures has to be determined in some objective way. Innovative procedures should be subjected to methodologically rigorous evaluation for *safety and effectiveness* at the earliest possible moment. The timing is important because a controlled, comparative study of a new procedure can become a very difficult and courageous undertaking if the innovation has already come to be viewed as a norm of medical practice. *Cost efficiency*, *social acceptability*, and *equality of access* are three subsequent thresholds to be crossed to establish a sound policy of public support and funding for medical innovations.[125]

What is the current clinical and public policy status of IVF and embryo transfer? Despite the continuing moral objection of some communities and persisting differences of view about criteria of eligibility as well as about ethical acceptability of certain uses of IVF and embryo transfer, early moral quandaries have largely ceded place to widespread social acceptance of these reproductive procedures. Social acceptance, however, is neither a reliable indicator of clinical status nor a sufficient basis for a policy of public support and funding.

Are the procedures of IVF and embryo transfer sufficiently *safe* to merit public support as treatments for infertility? There are four principal foci of attention for the question of safety: the mother, the embryo, the fetus, and the newborn child.

There is no evidence that women undergoing IVF and embryo transfer court any major risk of bodily harm. The risks associated with laparoscopy and the other procedures involved in IVF and embryo transfer are generally estimated to be minimal. These women, however, do court additional risks to health in the event of ectopic and multiple pregnancy. The current practice of multiple embryo transfer clearly increases the risk of multiple pregnancy, but it is unknown whether this practice "predisposes the ectopic pregnancy."[126]

There is also no evidence to date that IVF and embryo transfer lead to a higher rate of congenital birth defects than does pregnancy achieved by natural sexual intercourse. No congenital abnormalities were identified, for example, among the IVF and embryo transfer births (more than 100) recorded in the Australian National Registry of In Vitro Pregnancies during the first 18 months of its operation.[127] Persons involved with the Registry have, however, drawn attention to factors that could "predispose a pregnancy arising from IVF/ET to a potentially high risk of possible congenital malformation."[128] It should also be emphasized that judgments about the relative safety of IVF and embryo transfer in terms of associated rates of congenital malformations take time. Dr. John Biggers has stated that "during the first five years after birth the detection of severe congenital abnormalities increases by a factor of about three. It will be 3 or 4 years before the incidence of congenital defects in babies produced by *in vitro* fertilization and embryo transfer at age five will be known."[129]

As the number of IVF and embryo transfer births, now a thousand or more, increases throughout the world, public interest in the outcome of IVF and embryo transfer may decline. In the interest of sound public policy, however, data should continue to be systematically collected to permit an unbiased resolution of the safety issue.

The high rate of embryo loss after IVF and embryo transfer continues to be a focus of major concern. This loss may be due to the embryo's failure to implant after embryo transfer or to spontaneous abortion after implantation. Failure to implant and spontaneous abortion may be due to factors in the mother's body or to the deficient quality of the embryos that are transferred to the uterus. In either case, there are possibilities for improvement.

An embryo may fail to implant in part because of adverse hormonal and other changes in the mother's body, changes provoked by stress and some of the procedures used in IVF and embryo transfer. One practitioner has recommended:

> We should be encouraging the development of alternative methods of oocyte recovery (eg, ultrasound-guided aspiration, avoiding general anaesthesia and laparoscopy) and the transfer of embryos on hormonally optimal cycles, and that means encouraging work on embryo cryopreservation with a view to transfer at a time when maternal factors are more favourable.[130]

Increased attention is now directed to low-grade embryo quality as a primary cause of embryo loss. One study has estimated that "60% of embryos do not possess the potential for successful implantation."[131] Two researchers have attempted to circumvent the dilemma created by the need to assess the quality of embryos before transfer and the destructive effects of most methods of testing embryos. Dr. Douglas M. Saunders and Dr. C. O'Neill announced recently, "We have devised a non-invasive, non-destructive method of determining embryo quality in vitro (before transfer) and in utero."[132] The test involves measurement of a substance called "embryo-derived platelet-activating factor," or EDPAF. When embryos do not produce EDPAF or fail to produce this substance in sufficient quantity, pregnancy does not result. Use of this test could lead to a more judicious selection of embryos for transfer and might help in determining whether defective metabolic potential in embryos is "due to IVF procedure or represents the normal biological variation within the population of zygotes."[133] The designers of this testing technique conclude:

> EDPAF seems to be strongly correlated with the viability of embryos and their pregnancy potential and may provide, for the first time, a quantifiable, non-invasive means of determining which embryos are viable before transfer. It could also be a powerful tool for examining the effects of all aspects of the IVF and embryo transfer technique (ovulation induction, laparoscopy, oocyte collection, and in-vitro culture techniques) on the production of good-quality embryos.[134]

Are the rates of embryo loss after IVF and embryo transfer appreciably higher than those of natural, unassisted reproduction? Though public policy considerations require such a comparison, the conclusions from available studies are not unanimous. There is some controversy.

One recent study of unsuspected pregnancy loss in healthy women concluded that only 8 per cent of human pregnancies, as a proportion of conceptions, "are lost at such an early stage of development that the patients are unaware that conception has occurred."[135] This conclusion, criticized as an isolated finding of a study marred by a basic methodological flaw,[136] contradicts the greater volume of evidence indicating that early embryonic mortality is high.

Dr. John Biggers's review of studies on embryonic mortality concludes that 40 babies may be expected to be born from 100 naturally fertilized human ova.[137] The DHEW Ethnics Advisory Board identifies the efficiency of natural or unassisted human reproduction in the following way:

> One study estimates that in 16% of cases where human ova are exposed to sperm, fertilization fails to occur. When fertilization does occur, the rate of embryonic loss during the first week is estimated to be 18% and in the second week an additional 32%. According to this study, only 37% of human zygotes survive to be delivered subsequently as live infants.[138]

These estimates correlate closely with the results of a prospective study, published in 1980, that found the rate of post-implantation embryo loss to be at least 43 per cent in the women observed. The exact rate of early spontaneous loss of human embryos after unassisted fertilization is unknown and difficult to determine. This rate, one should recognize, would depend on the combined incidence of loss in both *recognized* and *unrecognized* pregnancies. The latter is particularly difficult to study directly. Nevertheless, one recent study found that "61.9% of conceptuses will be lost prior to 12 weeks. Most of these losses (91.7%) occur subclincially, without the knowledge of the mother."[139]

If the success or effectiveness of IVF and embryo transfer means a pregnancy resulting in the live birth of a normal baby, rates of success currently vary from centre to centre. Dr. Robert G. Edwards reported that the clinical pregnancy success rate at Bourne Hall rose from 16.5 per cent in 1980 to nearly 30 per cent in 1983.[140] One should note that a pregnancy is called "clinical" when there are definitive signs that a fetus is present in the uterus. Fetal heartbeat is one such sign. In 1983, the Norfolk Clinic described the transfer technique that resulted in a 21 per cent pregnancy success rate between 1981 and 1982.[141] When these and other factors are weighed, the trend of opinion today is toward acceptance of IVF and embryo transfer as an increasingly valid treatment for some kinds of infertility, particularly for infertility due to tubal problems. In the Warnock report, for example, the U.K. Committee of Inquiry into Human Fertilization and Embryology took the following position on IVF and embryo transfer: "It seems to us that the technique has now passed the research stage and can be regarded as an established form of treatment for infertility."[142]

This statement needs at least two clarifications. First, "passed the research stage" cannot possibly mean that all essential questions have been satisfactorily answered and that these procedures no longer need to be subjected to research. The continuing high rates of embryo loss as well as the varying and generally low rates of pregnancy success – the probability of any one treatment producing a child is still only 10 to 15 per cent even in the leading centres[143] – document the need for considerable research on oocyte maturation, oocyte retrieval, embryo culture, and the conditions of fertilization and embryo transfer.[144]

Second, the claim that IVF and embryo transfer "can be regarded as an established form of treatment for infertility" is far too broad. There are many forms of infertility, and IVF is only one among many infertility treatments. IVF and embryo transfer is certainly not an established treatment for all kinds of infertility.

The procedures of IVF and embryo transfer, even with the current relatively low rates of success, offer the best chance of pregnancy when infertility is due to tubal problems, such as double tubal occlusion, previous surgical removal of Fallopian tubes, conglomerate tumors, or thick-walled sactosalpinges (distension of uterine tubes).[145] Microsurgical repair or reconstruction would be the one rival or alternative treatment to IVF and embryo transfer for some of these conditions. Dr. Hugo C. Verhoeven has stated, however, "It is difficult to decide which treatment is most favorable for the individual patient, as no exact criteria of selection exist."[146] Research to establish criteria for a more precise selection of patients for one or the other of these treatments is required.

IVF and embryo transfer may also offer a reasonable alternative to AID when the male partner is affected by oligospermia. These procedures may also be the best medical treatment for infertility due to antisperm antibodies in the serum of cervical mucus of the woman.[147]

Caution and research are required before proposing IVF and embryo transfer as established treatments for infertility due to endometriosis (growth of endometrial tissue, which normally lines the uterus, in abnormal places, such as the ovaries) or cervical conditions and especially for infertility from an unknown cause, so-called idiopathic infertily.[148] Pregnancy occurs independently of any treatment in a considerable proportion of couples affected by these kinds of infertility.[149] Controlled studies are needed to evaluate the efficacy and the need of IVF and embryo transfer as treatments for these categories of infertility.

Policy recommendations on IVF and embryo transfer stand a better chance of being balanced and just if they are part of an overall policy on infertility. The concern of the Warnock report merits recognition: "We would not want to see IVF, with its present relatively low success rate, cream off all the resources available for the treatment of infertility just because it has the glamour of novelty."[150] A comprehensive infertility policy will focus controlled scientific evaluation on older treatments as well as on the new.

Cryopreserved embryos in the treatment of infertility. The endometrium of a woman treated for superovulation is often not in the ideal state for the immediate transfer of an IVF embryo. The synchronization of embryo transfer to optimal endometrial and hormonal conditions would increase the chances for a successful pregnancy, reduce the likelihood of embryo loss, and reduce the number of laparoscopic retrievals of ova with attendant stress that a number would have to undergo. The question of storing embryos by freezing has arisen in part with a view to achieving this optimal synchronization. The storage of human embryos would be useful in other situations and for other purposes as well.

The risks of multiple procedures and laparoscopies, risks that can be gauged, have to be balanced against the risks of embryo loss or damage caused by freezing and thawing techniques. These latter risks are difficult to gauge today because experimental data on the freezing and thawing of human embryos is relatively restricted in scope. One cannot simply extrapolate to human embryos the results of research and experience already acquired from the quite extensive cryopreservation of other mammalian embryos. Moreover, the question whether cryopreservation techniques possibly cause subtle damage to the embryo that will show up only much later after birth of the child cannot now be answered. Answering this question would involve at least long-term follow-up of such children, if not a long-term controlled study. To date, only several children have been born, and these are recent births, after having been maintained as embryos in frozen storage.

Many practical and reasonable objectives would favour a policy permitting the frozen storage of human embryos. As already mentioned, cryopreservation would enhance optimal synchronization of embryo transfer and greatly facilitate optimal synchronization if donated ova or embryos were being used in infertility treatment. Medical or familial events occurring after IVF might also necessitate a delay in embryo transfer. Moreover, frozen storage would facilitate the development of very early pre-implantation diagnosis of chromosomal, genetic, or other defects in the embryo. Opposition to the frozen storage of human embryos is based partly on the position that the embryo is an individual human being from the time of fertilization. In this view, the protection due the early embryo is not consonant with maintenance of human embryos in a state of suspended animation, with the damage caused by cryopreservation techniques, or with potential procedures that frozen storage would render possible.

There is a significant, even if insufficient, volume of experience and data available as a basis for a policy decision whether frozen storage of human embryos should be permitted. Cryopreservation has been carried out at the Queen Victoria

Medical Centre/Epworth Hospital in Victoria, Australia. Within this program, more than 300 embryos have been frozen, 130 embryos have been thawed, and 45 thawed embryos have been transferred since January 1982.[151] The Victoria Committee to Consider the Social, Ethical and Legal Issues Arising from In Vitro Fertilisation cites this information in its report (the Waller report) and states that 75 per cent of embryos show signs of cellular damage after freezing and thawing. Nevertheless, this damage does not appear to prevent implantation or pregnancy providing a sufficient number (more than four undamaged blastomeres) of undamaged cells are present after thawing. The available evidence seems to indicate that "the cells which remain undamaged take over and replace those which have been damaged to such an extent that they cannot subsequently divide."[152]

If cryopreservation of human embryos is permitted in IVF and embryo transfer programs in Canada, there will be a need for a policy on the storage of human embryos to regulate such issues as: the institutions authorized to carry out cryopreservation of human embryos, the duration of storage, and responsibility for decisions about subsequent uses of stored human embryos.

A comprehensive cryopreservation policy would also have to consider the possible advantages of cryopreservation of human ova rather than human embryos. There may be some wisdom in a recommendation that would favour research to develop effective methods for the frozen storage of human ova, to parallel current methods for cryopreservation of human sperm. Success in developing such methods would mean, as the Waller report has indicated, "that a comprehensive reappraisal of the reasons for undertaking the freezing of embryos would need to be undertaken."[153]

Donated ova and embryos. When adoption is impossible, is difficult, or would involve delays beyond the period of time desired for parenthood, ovum or embryo donation may offer a way for couples affected by certain kinds of infertility to have a child. These new forms of assisted reproduction might be contemplated in the following situations.

A woman may be unable to supply an ovum for the IVF procedure, either because of an ovarian disorder or because her ovaries are inaccessible for laparoscopic retrieval. In such cases, an ovum donated by another woman could be fertilized by IVF procedures, using sperm from the husband of the infertile woman, followed by transfer of the embryo to the infertile woman's uterus. Ovum donation would typically separate genetic motherhood from gestational and social motherhood.

Embryo donation is a variant of this procedure and might be considered when, for example, both husband and wife are infertile. A donated embryo, formed by IVF procedures from a donated ovum and donated sperm, would be transferred to the uterus of the infertile woman. This procedure combines AID with ovum donation.

The lavage, or nonsurgical transfer, method may replace IVF procedures for both ovum and embryo donation. The donor woman is artificially inseminated, either with sperm from an infertile woman's husband or, if he is infertile, from donor sperm. The resulting embryo is retrieved from the donor woman by lavage and implanted in the infertile woman's uterus.

Each of these approaches has its own particular clinical difficulties and risks. The need for a surgical procedure to retrieve the ovum poses the major risk for the donor in the IVF procedure, and the exact timing of donor and recipient cycles constitutes the major clinical difficulty. With the lavage procedure, the donor runs the risk of becoming pregnant if the embryo is not removed. The risks of harm increase in the event of an ectopic pregnancy. This approach also requires synchronization of lavage to the recipient cycle.

Ovum and embryo donation will inevitably raise familial, social, legal, and ethical problems similar to those encountered already in the practice of AID. These issues include:

- the selection and screening of donors
- donor anonymity
- the mutual rights and responsibilities of donors and recipients
- the need for and the dangers of secrecy and deception
- standards for recordkeeping
- confidentiality and regulation of access to records
- confusion about motherhood and fatherhood when the genetic, gestational, and nurturing components of parenthood are distributed among three or more persons
- the legal status of the child
- the later effect on the child of being separated from his or her biological roots

Most of these issues, of course, are not startlingly new. Any society familiar with the practice of AID will already have faced most of these problems, even if it has not resolved all of them satisfactorily. The issues require varying combinations of legal or professional regulation, education, and counselling. These matters, it is generally recognized, are too important and weighty in societal consequences simply to be ignored or left purely to private arrangement.

Prohibition is an option some might want to propose. Those so inclined should consider that it would be difficult not only to implement a policy prohibiting ovum and embryo donation in highly mobile societies but also to justify and sustain such a policy in communities where AID is already practised, regulated, and generally accepted. Prohibition would possibly be justifiable and feasible if ovum and embryo donation posed substantially different and more serious threats to the good of the child, family, and society than AID has ever done. The prevailing opinion, however, is that this is not the case. The common good will be best served by a policy that seeks simultaneously to protect all the genuine values brought into play by these new forms of assisted reproduction and to minimize the likelihood as well as the scope of undesirable and degenerative changes in the reproductive order.

Surrogate motherhood. The agreement or promise of one woman—called here the "surrogate mother"—to conceive, bear, deliver, and relinquish a child to another woman or couple is an essential characteristic of surrogate mothering. This reproductive arrangement can be carried out in a variety of ways.

The requisite ovum may come either from the surrogate mother or from the commissioning woman, that is, the woman who wishes to raise the child. The sperm could come from the husband or the male partner of the commissioning couple or from a donor. Insemination, depending on the circumstances and source of the ovum, could be either by sexual intercourse, AID, or a combination of IVF with either AID or AIH. The recipient woman could be either single or married and not necessarily affected by infertility. The surrogate mother need not be married or already have children of her own; she could, however, be both a wife and a mother. Surrogate mothering could be done purely for philanthropic motives, with or without reimbursement for pregnancy expenses, or for a fee over and above expenses. The concerned parties might enter this arrangement with or without the mediation of lawyers or other agents. The surrogate mother could remain anonymous or be known, perhaps even related, to the commissioning woman or couple.

Though all of these modalities are equally possible, they are not all equally frequent or typical of surrogate motherhood as currently practised. The surrogate arrangement is typically sought and proposed when a woman is affected by medical conditions or forms of infertility that render childbearing impossible. A woman may suffer from a combination of ovarian and uterine disorders that prohibit both conception and pregnancy. Another woman, able to produce ova adequate for fertilization, may be unable to bear a child either because she lacks a uterus, suffers from disorders that provoke repeated miscarriage, or is affected by medical conditions that would make a pregnancy dangerous for her health or life.

If adoption is impossible or excessively difficult, surrogate motherhood seems to be the only way for some couples affected by certain forms of infertility to have a child. The challenge is to devise a policy that can both honour this need and desire of couples and respond adequately to the concerns raised by surrogate mothering. Those who have examined surrogate motherhood thoroughly tend to agree that several of these concerns are substantially different and more serious than those encountered in AID or foreseen for the practice of ovum and embryo donation.

The surrogate mother arrangement seems to harbour an intrinsic dilemma. On the one hand, enforcing the contract or agreement could violate the mutual bond of mother and child. It is difficult for many to imagine forcing the separation of a child from its mother on the basis of an agreement made before conception, before the surrogate mother experienced the bonds of attachment that can easily intensify during pregnancy and become very strong at birth. This is particularly true if the surrogate mother is also the child's real genetic mother. The commissioning couple, on the other hand, is open to deep disappointment and frustration of hopes, hopes that have presumably intensified over nine months, if the agreement is not honoured and cannot be enforced.

The status of the surrogate mother contract or agreement raises the question of the status of the child. This is an important legal, societal, and ethical issue. To whom does or should the child belong? Will this question be resolved by following pre-established rules or case-by-case by considering the child's likely best interests? George J. Annas has stated:

> On the maternal side, it is the biological mother's baby. And if she wants to keep it, she almost certainly can. Indeed, under the proper circumstances, she may even be able to keep the child and sue the sperm donor for child support. On the paternal side, it is also the biological child of the sperm donor. But in all states, children born in wedlock are presumed to be the

> legitimate children of the married couple. So if the surrogate is married, the child will be presumed . . . to be the offspring of the couple and not of the sperm donor.[154]

Considerable sums of money, over and above pregnancy expenses, have already been requested, offered, suggested, or paid as honoraria or fees for the surrogate mother. It is a dominant concern that the surrogate arrangement, perhaps more than any other reproductive scheme, invites commercialization. Commercialization, in turn, endangers the relationship of parents to child as well as the human character of reproduction. Annas has cited this objection of one U.S. court:

> Mercenary considerations used to create a parent-child relationship and their impact upon the family unit strike at the very foundation of human society and are patently and necessarily injurious to the community.[155]

Commercialization increases the likelihood of exploitation. The fear is that the surrogate arrangement may lead to some women being used to fulfill the needs, and desires, or even for the mere convenience, of other women. The Warnock committee cited exploitation as one of its most serious concerns.

> In the first place we have all agreed that surrogacy for convenience alone, that is, where a woman is physically capable of bearing a child but does not wish to undergo pregnancy, is totally ethically unacceptable. Even in compelling medical circumstances the danger of exploitation of one human being by another appears to the majority of us to far outweigh the potential benefits, in almost every case. That people should treat others as a means to their own ends, however desirable the consequences, must always be liable to moral objection. Such treatment of one person by another becomes positively exploitative when financial interests are involved.[156]

An additional concern is the separation of a child's genetic and social identities. Are children seriously or permanently harmed by the truth, however long it is kept secret, that one or both of their parents are not their "real" or genetic parents?

In a symposium in 1973 on AID and embryo transfer, Dr. Massimo Piatelli-Palmarini emphasized the need to detect "the collapsing of the historical and biological web which constitutes the human person."[157] He emphasized what one may too easily forget, namely that "the whole concept of a person and his existential 'feeling-in-the-world' depends as much on the history of how he came into being and on awareness of all the bonds linking him with nature and his fellow men as it does on his having a healthy body and a well-balanced mind."[158]

These bonds linking a child with nature and the human community are not insignificant. One's genetic history links one to a network of persons. Grandparents, great-grandparents, and the collateral relationships of uncles, aunts, and cousins are integral strands in the pattern of human connections essential to one's sense of identity. One may suffer from a very shallow sense of personal identity if one's origins reach back no further than one's parents, however well-intentioned, dedicated, and loving they may be.

Some adopted children, it would appear, are deeply marked by the total split between their genetic and social identities. Some AID and surrogate-mothered children may be similarly marked by the partial split characteristic of the reproductive schemes within which they were conceived.

A society confronting the needs, desires, and concerns of surrogate motherhood faces the central policy question: Should surrogate motherhood be prohibited, left to private ordering, permitted and regulated, tolerated, encouraged, or discouraged?[159] Alexander Morgan Capron has cited the need to go beyond the "binary prohibit/permit approach."[160] This would require the realization that resignation to undesirable consequences or changes is not the only alternative to prohibition of new reproductive schemes. When certain applications or features of novel reproductive arrangments threaten to "undermine basic values or weaken important roles, we ought to make such challenges explicit and then mount the necessary efforts to counteract their undesirable effects."[161] This approach, rather than outright prohibition or unregulated laissez-faire, might be the most promising path for a policy on surrogate motherhood in Canada.

Use of the human embryo in research. A wide range of important research projects would require the use of the human embryo in ways that would disrupt its normal course of development, render the embryo unfit for implantation, or entail its destruction. Though the question of the moral status of the embryo arises in the setting of infertility treatment, the issue about the degree of respect due the embryo is most acute in the setting of research.

The ethical issue arises because procedures for in vitro fertilization result in spare embryos or can be used to construct human embryos for research. The possible and reasonable research projects are too numerous to list and describe in this study; however, the perfection of freezing and thawing techniques, the improvement of embryo culture methods, the development of pre-implantation diagnostic methods, the study of the causes of failure to implant and of the factors involved in the formation of congenital disorders are some of the more immediate objectives scientists would like to pursue. Should they?

The answer and policy recommendations largely depend on how one views the pre-implantation embryo. Some people place great moral weight on the process of fertilization. The resulting embryo is seen as an individual human being with potential. In this view any action that would damage the embryo, disrupt its normal course of development, or lead to its destruction is morally unjustifiable.

Taking another view, which has appeared in recent policy documents, people attach moral weight to the stage of embryo development corresponding to the end of the period of implantation, roughly 14 days after fertilization. Various reasons are advanced for seeing this stage as somehow more normative than the endpoint of the fertilization process. Some people use the term "individuation." They argue that human life after fertilization cannot yet be the life of an individual human being as long as twinning or the fusion of embryos is possible. In this view, research leading even to the destruction of the embryo could be judged ethically acceptable. Others would justify research even up to a later stage of embryoinc development, setting a limit at the point when the embryo or fetus becomes sentient in some fashion.

Whatever policy limitations Canadian society places on research uses of the human embryo, a clear distinction will have to be made between research procedures and possible future therapeutic interventions, however experimental and unvalidated, that may be attempted on the human embryo. This is particularly important in view of the frequent recommendations that embryos used in research should not be transferred to the uterus as a treatment for infertility.

IVF programs will undoubtedly increase in number in Canada during the next few years. It is highly likely that Canadian researchers will propose projects with valuable clinical or fundamental scientific objectives that will require research with the human embryo. There is a deep division of opinion in Canadian society about the status of the human embryo. The challenge is to devise a policy that will avoid arbitrary prohibitions or restrictions on research without ignoring the long-term cultural and societal consequences of potentially extensive research on the human embryo.

The elaboration of Canadian policy for research with human embryos could be well served by the establishment of a special working group to explore the needs for such research, the implications of the likely projects to be proposed, and the issues to be resolved. The mandate of such a working group could be extensive enough to cover the kinds of public education required to keep the general public in step with the advancing frontiers of biomedical science. (The education aspect of this proposal is discussed in greater detail in the section Communication and Public Education in Chapter 4.)

Conclusion

For thouands of years an aura of mystery, some would say benign mystery, enveloped the entire phenomenon of human reproduction, the period of pregnancy, the blissful or tragic moment of birth. Mystery meant at least this: technical inaccessibility. Sperm and ova, zygote, embryo, and fetus were hidden within the human body. The human body and the need for sexual intercourse to unite spermatozoa and ova served both as a shield against imaginative manipulative designs and as a barrier to innovative therapeutic interventions.

All this has changed radically. We can now observe, manipulate, and experiment with the elements of human life in numerous novel ways. Applications of new techniques to human reproduction are gradually taking us to the frontiers of enormously powerful control over the origins of human life. It has taken human beings a long time to work out the customs, ethics, and laws appropriate to traditional forms of human reproduction. Technology today permits a rapid move away from these longstanding traditions. Will we just as rapidly arrive at a new reproductive wisdom to replace the old?

Chapter 2:

Prenatal Diagnosis

Maurice A.M. de Wachter

> A clinical practice based on scientific and technologic capacities alone is not equipped to deal effectively with the social, economic, ethical, and legal issues engendered by modern medicine and biology. . . . The normative problems of genetic counseling seem especially exigent, partly because there is no public or even medical agreement about the idea of intervening in human genetics.[1]

Introduction: Genetics and Medicine

The twentieth century will probably be remembered, in a medical sense, as the century of genetics and human disease. As early as 1902, Sir Archibald E. Garrod, a physician, listed the first-known inborn error of metabolism, alkaptonuria, a metabolic disorder that manifests itself in urine, which, upon contact with air, turns inky black. In this way the concept of Mendelian recessive inheritance was first applied to man.

Another big step in prenatal diagnosis was taken in the early 1950s, when amniotic fluid was analysed to predict the severity of Rh-hemolytic disease in the newborn. In some cases this diagnosis led to intra-uterine transfusion. In the late 1950s, chromosomal disease was discovered, and this discovery was soon followed by another giant step: tissue culture and the cultivation of fetal cells, a development that resulted in prenatal detection of genetic disease.

Interest in the prenatal diagnosis of genetic defects has grown remarkably since the mid-1970s. Researchers are now able to determine whether a fetus is at risk to some specific genetic disease and whether it actually has that disorder. In the latter situation, parents are faced with deciding whether or not they wish to continue the pregnancy. Demand for prenatal diagnosis is on the rise.

In 1981 the known list of hereditary disorders numbered 3000; this list grows at a rate of about 100 newly identified disorders each year. Only 165 of these fetal disorders can be diagnosed prenatally. Moreover, no cure exists for genetic diseases; the only recourse is treatment to prevent the disease from developing further. The dramatic discrepancy between the growing numbers of diagnosable diseases and the lack of effective treatment is one of the major deficiencies in genetic services today. It reveals itself in the quite common opinion that detection of a defective fetus too often leads to a decision to abort. Even the triumphant statement "that the fetus with a treatable birth defect is on the threshold of becoming a patient"[2] must be taken with a grain of salt.

The Genetic Model in the Study of Disease

The relationship between genetics and medicine has been presented, in an authoritative Canadian report, as evolving from a purely medical to a more genetic model. In the past, the medical model on health and disease prevailed. Environmental factors such as nutritional deficiency and infections were dominant in studying the causes of disease. Diseases were controlled by combatting their cause (public health) or by mobilizing a cure (therapeutics). "As a consequence, diseases in which a genetic component is prominent are now on the ascendancy, and their control will require a different approach."[3]

The new genetic model views health as a state of equilibrium and disease as disequilibrium in the relationship between organism and environment. Between balance and imbalance lies a spectrum of possibilities that is useful in planning the prevention and treatment of a particular illness.

Chromosomal aberrations and most of the Mendelian disorders are located at the genetic end of the spectrum because they have always expressed themselves, whatever the environment. In the middle are diseases in which a particular gene expresses itself only in a specific environment. Here we find pharmacogenetic diseases (in response to drugs) and multifactorial diseases (arising as the result of the interaction of several genes). At the environmental end of the spectrum are the diseases in which particular agents such as poisons act on the universal genotype.

In revising their approach to the origin and cause of illness, physicians and medical researchers have developed a new method, of which the basic tenets are:

- Every disease has both environmental and genetic components.
- For every genetic component one or more markers exist. (This means that direct products of genes can be recognized; for example, a person who has B18HLA antigens is more likely to develop hypertension.)
- Environmental factors can be tracked down and isolated.
- No portrait of a disease is complete without a thorough understanding of both genetic and environmental factors and the way they influence its course.[4]

Despite this accumulation of evidence showing the mutual importance of genes and environmental factors in disease, the perception persists that diseases have either "genetic" or "environmental" causes. Even in an age of "new genetics," genes do not act in a vacuum. Interaction of genes and environment may vary. Persons may vary in their degree of susceptibility, itself a variation with a genetic basis, but variation always occurs within an environment. Indeed, "all our experience tells us that in fact diseases are not unitary in either cause or expression."[5]

As with all new approaches, the genetic model knows many a struggle within and without. Clinical and social acceptance are reflected in an increasing number of research grants and in the public's demand for access to the genetic services of prenatal diagnosis, and to the screening programs. The underlying moral assumptions – as well as the emphasis on prevention, diagnosis and therapy – make genetic services an issue for which society must assume responsibility. Decisions on the promotion and management of these are needed.

The goals of genetic medicine, particularly prenatal diagnosis, will have to be reformulated as new developments take place. It is easy to ignore those who doubt whether prenatal diagnosis will serve any purpose other than screening, selecting, and rejecting the defective fetus. Indeed, in 95 to 98 per cent of diagnoses, the fetus appears to be unaffected. To ignore these doubts may, however, be a wrong and, in the end, a counterproductive policy.

Genetic Disease

The prevalence of genetic factors in human disease has been expressed in the following general estimates, which the authors considered to be "not unreasonable."

Chromosomal mutations occur in:

- 50 per cent of all spontaneously aborted fetuses

- 5 per cent of all stillbirths and infants dying within one week after birth
- 5 per 1000 surviving live births.

Genetic variation with possible handicaps in a lifetime occurs in:

- 10 per cent of all live-born infants.

Of all pediatric hospital admissions:

- 12 per cent are for single gene, chromosomal, and multifactorial disease
- 18 per cent are for multifactorial, congenital malformation.

Of all adult hospital admissions:

- 12 per cent are for disease with a significant genetic component.

Of all severe mental retardation:

- 15 per cent of diagnoses are Mendelian
- 45 per cent reflect a genetic component.[6]

In the United States, the so-called genetic diseases were singled out in a report by the National Institutes of Health (NIH) as the second leading cause of infant mortality, with at least 20 per cent of all infant deaths attributed to genetic factors. Genetic disorders are the second leading cause of death in the one- to four-year age group, as well as an important cause of infant and childhood morbidity (mental retardation, physical disability). The report concludes that diseases resulting from such components constitute a major challenge to the American healthcare system.[7]

According to the U.S. Department of Health and Human Services, more than 15 million Americans suffer from one or more types of birth defects, 80 per cent of which are thought to be caused by genetic changes. Life-years lost through genetic diseases are estimated to be six and one half times as many as those lost through heart disease.[8]

Public policy making requires classification of genetic disease because the policy questions and their solutions will vary depending on: the nature of the disease; how it is inherited; whether it is lethal and, if so, at what point in life; whether it is simply handicapping and, if so, in what way; whether it is found largely in one ethnic group and, if so, in which one; and whether treatment is possible and, if so, how easy and how expensive it is.[9]

Human genes are located along the 46 chromosomes, 23 of which every conceptus receives from each parent. Forty-four of these chromosomes are "autosomes," similar in males and females. These autosomes are arranged in 22 pairs. Each parent offers a single sex chromosome, resulting in XX (girl) or XY (boy). Table 2-1 is a schematic presentation of several authors' attempts to categorize genetic diseases, their mode of inheritance, their absolute frequency, and their relative ethnic prevalence.[10]

Treatment for the nearly 3000 genetic diseases is generally poor, with a few exceptions. It is sometimes possible to prevent the birth of defective fetuses, provided that the defect is detectable through prenatal diagnosis. According to the latest update in June 1980, 165 separate fetal conditions, excluding chromosomal aberrations, have been reported diagnosed in utero.[11]

Treatments for Genetic Disease

According to two researchers, "there is nothing intrinsically special about genetic diseases that makes them untreatable."[12] Because of the great number and variety of genetic disorders, however, almost no effective treatments exist. Prevention remains the most effective treatment, although spontaneous mutations are not altogether avoidable. For mutations that have been transmitted, prevention takes on the shape of "genetic screening, counselling, artificial insemination, amniocentesis, abortion, and so on."[13]

Three therapies are available for those born with a genetic disease. First, *the physical environment* may be altered to make the affected person more comfortable. One could, for example, avoid environmental settings that cause allergies or chronic lung diseases. Second, *the diet* may be modified to supplement a deficient metabolite or to restrict a toxic substance. The classic example is the patient with phenylketonuria (PKU), for whom diet restriction from birth will prevent the disease from developing. Third, *the internal environment* may be changed by drugs or surgery. Immunological incompatibility between an Rh-negative mother and an Rh-positive fetus is largely due to the presence of the D antigen, one of several antigens of the Rh system, in the fetus. Hemolytic disease of the newborn can be prevented by injecting the mother with antibodies to this D antigen. Also, surgical treatment of some birth defects ameliorates the problems related to these defects.[14]

These three treatments take care only of the consequences of genetic diseases. Treatment would be more effective if the intervention could take place one step less removed from the defective gene or genes. The current interest of researchers therefore lies in providing the products of the genes, that is, the proteins, themselves.

TABLE 2-1
Categories and Characteristics of Genetic Diseases

Category & Number	*Mode of Inheritance*	*Example*	*Frequency*	*Ethnic Prevalence*
Autosomal recessive 1117 listed	Individual receives two genes found at the same position on a common parental autosome.	Phenylketonuria (PKU)	25 per 10 000 newborns (that is, 1 in 4 children of carriers)	1 in 60 whites carries the gene for PKU.
		Tay-Sachs		1 in 30 Eastern European Jews carries the gene for Tay-Sachs.
		Sickle-cell anemia		1 in 12 Blacks carries the gene for sickle-cell anemia.
Autosomal dominant 1489 listed	A single gene from either parent causes the disease to manifest itself, or the disease occurs as a spontaneous change (mutation).	Huntington's disease	6 per 10 000 newborns (i.e., 1 in 2 children of carriers)	none
X-linked (recessive or dominant) 205 listed	A single gene from the mother causes expression of the disease only in males.	Hemophilia A, B	1 in 10 000 males	none
		Duchenne's muscular dystrophy		
Multifactorial	Origin and genesis are due to both genetic and environmental factors.	Diabetes	165 per 10 000 newborns	none
		Neural tube defects, e.g., spina bifida		
		Congenital heart malformation		

Sources: Marc Lappé, *Genetic Politics: The Limits of Biological Control* (New York: Simon and Schuster, 1979), pp. 22 ff.; A.P. Mange and E.J. Mange, *Genetics: Human Aspects* (Philadelphia: Saunders College/Holt, Rinehart and Winston, 1980); J.J. Nora and F. Clarke Fraser, *Medical Genetics, Principles and Practice* (Philadelphia: Lea and Febiger, 1981).

Diabetes, hemophilia, and dwarfism are effectively treated by supplying insulin, factor VIII, and growth hormone, the production of which is either totally or partially deficient in the bodies of persons affected by these abnormalities. Such treatment is, however, complicated and expensive. Recent successes in the production of recombinant DNA of human proteins are promising for further clinical applications within a few years. Further down the road improvements in organ and tissue transplantation (kidney, thymus, bone marrow) are to be expected.[15]

The impressive variety of therapeutic approaches, that is, of avenues that may lead to treatment, should remove any pessimism over the possibility of treatment for genetic diseases. Most treatments are, however, very expensive, requiring sophisticated medical, biochemical, and technical expertise. Who is to pay for them will be a matter of continuing debate.[16]

Complete cure of genetic disease is expected to come from two stages of gene therapy. First, physicians treat somatic cells (the cells of the body) by providing normally functioning alleles (the alternative forms of the genes) to those who suffer from genetic disease. Second, changing the germ cells of such persons means that the children of these patients will also be free from disease. For the time being, the hopes given by gene therapy are restricted to single-gene defects, for example, blood disease. Disorders caused by chromosomal aberrations, such as Down's syndrome, and multifactorial traits would not be cured by gene therapy. "Likewise, characteristics such as personality and intelligence, are probably outside the realm of this technique's potential"; thus, French Anderson concludes his survey of the potential and limitations of gene therapy by saying that "gene therapy remains a promising, but not yet available, technology."[17]

To arrive at a reasonable and socially acceptable answer to the management of genetic diseases, policy makers must compare the answers and weigh the feelings of those who run genetic centres and services, of those who will or will not procreate under these conditions, and of the community at large. The policy choices for selecting, rejecting, or treating defective offspring should be defensible, explicable, and rational, both scientifically and socially.

Genetic Counselling and Prenatal Diagnosis: State of the Art

The management of genetic disorders and disease has become a major challenge to our society. Professional geneticists themselves prefer to use the strictly medical and technical management techniques of prenatal diagnosis. In the wider stream of genetic counselling, the application of these techniques was the very first of all genetic services.

Genetic Counselling

Genetic counselling provides advice about the occurrence of genetic disorders and the risk of recurrence of a defective fetus. Counsellees are informed of existing services, techniques, and alternative choices. M.W. Shaw has listed some of the objectives of genetic counselling as follows:

1. Directed at the affected individual
    a) Decrease the pain and suffering of the disease.
    b) Advise if treatment is possible.
    c) Quote risk figures for offspring and other relatives.
    d) Reduce anxiety and guilt.
    e) Help patient to cope with the affliction.
2. Directed at the parents
    a) Help couples make rational decisions about their reproduction.
    b) Give family planning options to at-risk matings.
    c) Reduce anxiety and guilt in the parents.
    d) Educate the parents about the disease in question.
    e) Encourage couples to make their own decision.
    f) Discourage high-risk couples from reproducing.
3. Societal goals
    a) Eliminate genetic disease.
    b) Prevent genetic disease.
    c) Reduce the incidence of genetic disease.
    d) Reduce the burden of genetic disease.
    e) Decrease the frequency of deleterious genes.
    f) Upgrade awareness of genetics in the public.
    g) Influence mate selection.[18]

This list is not exhaustive, nor does it express consensus among geneticists. Some geneticists will reject several of these stated aims, such as discouraging high-risk couples from reproducing. Some objectives, such as "eliminate genetic disease," are considered unrealistic, because recessive disorders will never be eliminated. Still other goals need refinement: some people think, for instance, that geneticists should not merely encourage but also assist couples in making their own decisions.

Nevertheless, the list clearly indicates that genetic services are not only directed toward individuals, parents, relatives, and society, but also reflect and express the interests of all of those concerned. Consequently, public policy makers may become interested in the activities performed by genetic counsellors, such as:

- recording the family pedigree
- verifying the diagnosis of affected relatives
- determining the applicable genetic facts
- recognizing and dealing with the psycho-social implications of prenatal diagnosis
- discussing the potential problems of undergoing prenatal diagnosis with its various techniques
- discussing the decision a couple makes if the fetus is defective.[19]

The Techniques of Prenatal Diagnosis

Prenatal diagnosis is performed through a variety of techniques. Some show the fetus directly or indirectly, while others allow one to collect fetal blood, skin, or samples of the amniotic liquid, which are then analysed. A distinction may be made between "information" techniques, such as amniocentesis or fetoscopy, and "interpretation" techniques, such as karyotyping, enzyme assays, and DNA analysis.

All of these techniques have different functions in the detection of either chromosomal, metabolic or structural disorders. The following sections present a comprehensive description of each technique necessary to review the state of the art and an evaluation of its clinical status, use, and safety.

Amniocentesis. Amniocentesis-from the Greek words "amnion" (the fetal membrane) and "kentesis" (pricking or puncture)-involves the insertion of a needle into the sac surrounding the fetus and the withdrawal of some of the amniotic fluid. The procedure takes place at 14 to 16 weeks of gestation (menstrual age). The amniotic fluid contains fetal cells, which, after culture, may be analysed for fetal enzyme activity and for fetal chromosomes. This process allows the detection of several biochemical and chromosomal disorders.

Some biochemical analyses can be performed on the fluid itself, as in measurements of alpha-fetoprotein (AFP) for neural tube defects. Spina bifida with myelomeningocele, that is, the protrusion of the spinal cord through a defect in the vertebral column, can be discovered in this way.

Amniotic cells grown in culture also permit biochemical detection of inborn errors of metabolism. Tay-Sachs disease, for example, can be detected in this way. Cultured cells can also be used to prepare karyotypes, that is, to display human chromosomes to analyse their number, form, and size, as well as their grouping. In this manner, trisomy 21, or Down's syndrome, can be detected.

One serious disadvantage of cell culture in prenatal diagnosis is that it takes two to four weeks of culture growth before there are sufficient cells for analysis. Microtechniques that require a smaller number of cells and less time will soon be introduced. The chorion villi sampling (CVS), in particular, is a recent and very promising technique because it can be performed at 8 to 12 weeks of pregnancy.

In 1979 the NIH declared amniocentesis to be "no longer experimental, but part of standard medical practice."[20] As in any medical procedure, however, there is a risk: in this case, loss of the fetus. However small the risk, specialists are concerned about it and recommend ultrasonic examination before and during amniocentesis to avoid complications. Similar and even higher risks of fetal loss have been reported in CVS.[21]

Ultrasound. The human fetus has for centuries remained a medical recluse in an opaque womb. With ultrasound, one can now visualize the implantation site and fetal anatomy: limbs, organs, and certain major skeletal defects. Certain heart malformations and other deformities, such as cleft palate, may soon be added to the list.[22] Ultrasound is a noninvasive technique that appears to be safe for both fetus and mother.

According to a *Lancet* editorial, ultrasonography has now largely replaced diagnostic radiology in modern obstetric practice.[23] Where the most modern facilities are available, all patients are screened during the first half of pregnancy to assess gestational age, to diagnose multiple pregnancy, to identify nonviable pregnancies, to locate the placental site, to study fetal dynamics, and to detect fetal abnormalities. Recently, neural tube defects have been identified by this process, and ultrasound has become a supportive technique in measurement programs for alpha-fetoprotein.

A report for the U.S. House of Representatives lists the following disorders detectable by ultrasound:[24]

- anencephaly
- ascites
- chrondroectodermal dysplasia
- diaphragmatic hernia
- duodenal atresia and jejunal atresia
- encephalocele
- enteric cyst of thorax
- gastroschisis and malrototion
- hydrocephaly
- hydronephrosis, megalureter, urethral obstruction
- infantile polycystic kidney disease
- lymphagiectasia
- meconium ileus (cystic fibrosis)
- meningomyelocele (spina bifida)
- omphalocele
- porencephaly
- renal agenesis
- renal dysplasia
- roberts syndrome
- short limb skeletal dysplasia
- thanatophoric dysplasia.

Disadvantages and risks seem to be rather small for ultrasonic imaging of the fetus. With this technique gaining in popularity, a proper assessment will be necessary to follow up its effects on the fetus and, later, on the infant. As yet, no difficulties have been observed, and there are no reasons to expect any serious problems. Yet, a letter in the *Lancet*, responding to the editorial mentioned above, turned the argument around. The author asked for references to "a properly controlled statistically significant long-term follow-up of infants exposed to ultrasound *in utero*."[25]

Fetoscopy. For centuries the fetus not only was invisible in an opaque womb, but also was altogether untouchable. Now fetoscopy, using a fibreoptics system, offers a direct, albeit limited view of the fetus. The aspiration of blood or skin samples for analysis is also possible. Thus, researchers can obtain new information about the brain, the structure and function of the liver, hemoglobin from red blood cells, and hormones from the various endocrine glands. These elements cannot be measured using amniocentesis.

Fetoscopy has a few major limitations, which have prevented it from being used extensively. Geneticists recommended that "fetoscopy be performed in academic research centres in conjunction with counselling, ultrasound and an adequate patient base to justify its use and development."[26] Fetoscopy will not reach the status of standard medical practice as long as it remains an invasive procedure with limits in visualizing and with risk to the fetus. As its safety improves, however, this technique could be used for chromosomal and biochemical analysis of fetal blood cells instead of cultured amniotic fluid cells. This would allow prenatal diagnosis even when the pregnancy is too advanced to be terminated.[27]

The real breakthrough, however, came in 1982 with chorion biopsy, or CVS. Under the control of ultrasonic scanning, the fetoscope is introduced through the vagina into the uterine cavity, and a biopsy of chorionic tissue, at the outermost of the fetal membranes, is taken. The cells obtained can be used for efficient, direct chromosome studies and enzyme determination. The major advantage of this method is that it can be used during the first trimester of pregnancy. Short- and long-term risks, however, have yet to be thoroughly assessed.[28]

Alpha-fetoprotein measurements. It was demonstrated in 1972 that elevated levels of alpha-fetoprotein in the amniotic fluid indicated the presence of anencephaly (a lethal defect of the brain), or encephalocele (the protrusion of brain through the skull), or spina bifida (protrusion of the spinal cord). By 1979 it was estimated that at least 75 per cent of the 15 000 amniocenteses performed in the United States had a routine AFP assay on amniotic fluid, whereas maternal serum screening was still very limited. In less than ten years, "alpha-fetoprotein determinations have become the cornerstone of counselling for neural tube defects."[29]

Alpha-fetoprotein is a glycoprotein that resembles albumin. The level of AFP in fetal serum rises rapidly through the thirteenth week and then declines. This protein is excreted with the urine into the amniotic fluid and diffused into the maternal serum. Consequently, the AFP measurements apply to AFP levels in both the amniotic fluid and the maternal serum. As a result AFP measurement is the first technology applicable to the entire pregnant population. Pregnant women normally have a certain degree of AFP elevation. However, "when the level increases more than 2.5 times the expected median (at 16 to 18 weeks), there is a serious possibility of an open fetal neural tube defect (NTD), anencephaly or spina bifida."[30]

AFP in maternal serum may be caused by a whole range of other factors, not all of them necessarily pathological. Maternal serum levels may be high in a normal pregnancy, such as in twinning, or through underestimation of gestation age, particularly for other diagnoses of development defects in the fetus. It is often difficult, however, to determine the incidence of high AFP serum levels. Such is the case in fetal death, congenital nephrosis, hydrocephalus, and Turner's syndrome, among others.[31]

For all these reasons, the predictive value of a positive result for a single maternal serum test indicates only a 1 in 30 probability of having an NTD. A second serum test is, therefore, needed through amniocentesis guided by sonography.

The fact that retrospective amniocentesis, that is, for mothers who have already had a child with NTD, detected only 10 per cent of all affected fetuses is another reason to welcome maternal serum measurements of AFP. "This raised the possibility of screening all pregnancies routinely."[32] Both specificity and sensitivity of the test on maternal serum are, however, lower than they are when applied to amniotic fluid, hence the difficulty in determining whether a routine screening program is advisable.

A report on this matter by the Council of Scientific Affairs of the American Medical Association compares the risks of an amniocentesis with the results of a maternal serum AFP-monitoring program. The first risk is the possible contamination of the amniotic fluid with fetal blood. If this happens, an additional test for hemoglobin is required. The second is abortion or fetal loss attributable to amniocentesis. Thus, AFP screening of all pregnant women in the United States would yearly entail amniocentesis for 51 000 women to detect 2300 defective fetuses. Unintended fetal loss, calculated at 1 per cent, would cost about 500 normal fetuses. Another price to be paid for such a screening program is the psychological stress of patients with false-positive serum-test results. For each aborted fetus with NTD, about 25 mothers would have to undergo this stress. The panel of consultants who assisted in the preparation of the report concluded that "maternal serum AFP screening of all pregnant women should not be advocated at this time."[33]

DNA technology. Locating the positions of the genes on any given pair of human chromosomes has always been seen as having great practical significance for human and medical genetics. Whereas gene mapping was formerly, a very laborious process, the latest DNA technology, using techniques such as restriction enzymes and linkage analysis, has rekindled the interest of geneticists.

Restriction enzymes are useful because they digest the fetal DNA, obtained from amniotic fluid, in highly specific ways.

These enzymes will cut DNA at specific sites that then become reference points for the location of genes. Geneticists have thus been able to determine the genotypes (the genetic makeup) of fetuses at risk for sickle-cell anemia in about 60 to 80 per cent of all risk families. This technique requires only a small amount of amniotic liquid and takes very little time (approximately one week) to provide results.

Linkage analysis is a DNA technology that allows one to deduce the presence of a genetic disorder even though the locus cannot itself be directly detected. This deduction is made possible by the presence or absence of a closely linked gene that is otherwise of no medical consequence.[34] Hemophilia, for example, cannot be diagnosed in a fetus now, but G6PD can. For mothers at risk, the determination of a gene product called G6PD in a male fetus will indicate with considerable accuracy if the fetus will be hemophiliac.

Both technologies of restriction enzymes and linkage will eventually lead to complete mapping of human genes, making possible the diagnosis of every single genetic disorder. Diagnostic ability is thus about to make a quantum jump. DNA technologies "represent an extremely exciting strategy for the prenatal diagnosis of genetic disease."[35] Eventually, standardized libraries of cloned probes for known segments of the genome, that is, the complete set of hereditary factors contained in the chromosomes, will be available.[36] The potential of this procedure is very promising, not only for the detection of fetal deficiency, but also for determining whether a future pregnancy will demand amniocentesis. Moreover, individuals at risk for heritable disorders that express themselves late in life ought to be able to determine if they are at risk before the obvious symptoms are revealed.[37]

Huntington's disease, a progressive neurodegenerative disorder with first symptoms occurring only between age 30 and 50 is a noteworthy case in point. Because of the late onset of this disease, most people have children before they realize that they have inherited Huntington's chorea. There is no reliable method for prenatal diagnosis of the disease and no effective treatment. Toward the end of 1983, it was shown that the Huntington's disease gene is linked to a polymorphic DNA marker that maps to chromosome 4. This localization is the first step in using recombinant DNA technology to identify the primary genetic defect in this disorder. "Understanding the nature of the genetic defect may ultimately lead to the development of improved treatments."[38]

Outlook

Beyond the developments reflected by the increasing number of detectable disorders through prenatal diagnosis, the medical literature on genetics shows the profound interest of geneticists in developing more reliable, more refined, more specific, and less invasive techniques. An instance of a less invasive technique was reported in reference to the assessment of fetal condition in severe rhesus immunization. Instead of a fetoscopy-guided approach for direct puncture of the umbilical cord, doctors measured the blood flow in the umbilical vein by combining the techniques of pulse Doppler and ultrasound.[39]

To the increased list of detectable thalassemias (blood diseases), geneticists are now working to add cystic fibrosis. Cystic fibrosis of the pancreas, a disease that causes death in childhood or young adulthood, is a genetic deficiency with a still unknown, underlying molecular defect. It is the most common recessively inherited disease in Caucasians, with a frequency of about 1 in 2500 births. There is little doubt among geneticists that cystic fibrosis is next in line for prenatal diagnosis. According to Nadler and Walsh, current procedures provide a practical and reliable approach for the intra-uterine detection of cystic fibrosis.[40] Most geneticists, however, would not use this "relative" test except with extreme caution, since it will give a certain number of false negative diagnoses. Once established as standard practice, the cystic fibrosis test would certainly expand prenatal diagnosis considerably. Techniques for the recognition of carriers are being developed simultaneously. They will permit the identification of high-risk mating and enable screening for the disease, even though the mechanism of the underlying molecular defect is still not understood.

Indications and Goals in Prenatal Diagnosis

Survey

One aim of prenatal diagnosis is to reassure parents at high and unacceptable levels of risk that the fetus is unaffected. This fundamental goal of prenatal diagnosis, shared by geneticists, is loaded with assumptions, some quite obvious, others less so.

"Prevention" after detection of a defective fetus means, for example, preventing the birth of a defective baby. Although the proportion of such preventions has never been established, many parents, particularly pregnant women, object to this outcome. They find prenatal diagnosis either premature, valid alternatives such as treatment and cure are not available, or too late, because they consider the price of fetal life too high to pay for the promised reassurance.

Some physicians have questioned whether it is good medicine to offer a genetic service, now well into its second decade, that promotes "good" life through screening and rejects its defective forms. In an article reviewing the current status and future prospects of prenatal diagnosis, Benzie states that "prevention and treatment, not abortion, should be the aim of antenatal genetic diagnosis."[41]

The editor of the *New England Journal of Medicine* was disturbed by a brochure of the Tay-Sachs Prevention Program that read: "A simple blood test can prevent Tay-Sachs disease. Detection and counselling enable carrier couples to have children free of this disease." He criticized such advertising for not making clear "that the only way for the couple to have children free of the disease is by amniocentesic tests and then abortion. The couple can have normal children only by killing off all the affected fetuses."[42]

Meanwhile, prenatal diagnosis has increased 50-fold since the early 1970s. There can be no doubt that it meets one of the fundamental aspirations of our time: to control fertility, both the number and the quality of infants born. Furthermore, prenatal diagnosis puts this control very much in the hands of women. From now on they may consider it their right to negotiate with their partners, with professionals, and with society the exact conditions under which they will assume the social responsibility of procreation. Is it then a physician's affirmative duty to increase access to prenatal diagnosis? Is it society's duty to make policies that will support increased access to prenatal diagnosis?

Finally, to say that prenatal diagnosis is for women at high and unacceptable levels of risk presupposes that terms have been defined. Over the years both notions have been transformed into indication (the circumstances determining treatment), the key that opens the gate and gives women access to prenatal diagnosis. But is the notion of high and unacceptable risk a scientific, a medical, a social, or an emotional notion? The problem of defining indications is well illustrated in the on-going debate over maternal age (40, 38, 35, 32 . . .) and the cut-off point for accessibility to the services.

Indications for Prenatal Diagnosis

Advanced maternal age is the most common indication for amniocentesis. Indeed, a strong connection has been established between advanced maternal age and the birth of offspring with chromosome deformations.[43] A recent report of a Montreal hospital reviewing 3228 amniocenteses found that advanced maternal age (39 and over) was increasingly the reason women asked for amniocentesis. Findings of a study on these statistics are shown in Table 2-2.[44]

TABLE 2-2
Reasons for Amniocentesis (1971-1980)
(%)

Reasons	*1971-1979*	*1979*	*1980*
Advanced maternal age	43	54	52
Neural tube defect	21	19	20
Trisomy 21 in previous child	15	11	9
Trisomy 21 in family	6	7	6
Metabolic disorder	2	2	3
Other	13	7	10

Source: Louis Dallaire et al., "Le Diagnostic prénatal des maladies génétiques au second trimestre de la grossesse," *L'union Médicale du Canada* 111 (avril 1982), p. 301.

The risk of detecting an affected fetus is, according to maternal age groups, 1 per cent for age group 35-36, 5 per cent for 40-41, 8 per cent for 42-43, 11 per cent for 44-47. The authors responsible for these statistics point out that "the age at which the risk becomes high enough to be an indication for amniocentesis is a question of policy that varies from centre to centre."[45] This is undoubtedly true. Perhaps one should take the question a step further. To say that the matter has to be decided between a woman and her doctor is indeed a controversial if not a debatable statement. Second, one may ask whether such policy ought to be left to genetic centres or whether medical associations, governments, and society at large should have their say in the matter. The Comité de Déontologie de l'Association des Médecins de Langue Française du Canada published a paper on prenatal diagnosis with a series of recommendations and conditions necessary for responsible management of prenatal diagnosis.[46]

Advanced maternal age is but one of several indications for prenatal diagnosis. In medicine, indications generally reflect the efforts of professionals to justify, order, and decide upon their current practice. Indications are the crystallization of many factors, such as the seriousness of a disease, frequency, recurrence, urgency, and chances of successful therapy. For amniocentesis, the probability of occurrence or of recurrence often seems to be the standard by which the acceptability of the procedure is measured. The argument is as follows. Amniocentesis adds 1 per cent to the already existing risk of spontaneous abortion and 1 per cent to the risk of neonatal problems. "If the probability of occurrence is greater than the 1 to 2% probability of damage from the procedure," Fraser has observed, "the procedure is justified."[47] Commenting on indications for amniocentesis, he adds: "Just where the cut-off point should be is a matter of judgment, and there are no hard-and-fast rules. For the individual case the most important factor is the parents' view of the risks and benefits; for society, questions of cost and the distribution of resources complicate the picture."[48]

Recent surveys of literature mention the following indications of occasions when, it is generally thought, physicians ought to discuss amniocentesis with their patients:[49]

- pregnancies in women 35 years of age and over
- a previous pregnancy that has resulted in the birth of a chromosomally abnormal offspring (for example, a previous child with Down's syndrome)
- a known chromosomal abnormality in either parent (for example, when either is a translocation carrier, that is to say that one piece of a chromosome is transferred to another chromosome, thus increasing the chance of a chromosomally abnormal offspring)
- advanced paternal age, though this indication is still controversial

These four indications account for 85 to 95 per cent of all prenatal diagnoses. The remaining 10 to 15 per cent includes a variety of genetic indications, such as:

- history of multiple (three or more) spontaneous abortions in this marriage or in a previous mating of either spouse
- previous birth of a child with multiple major malformations in which the chromosomes had not been examined
- women who have near relatives with Duchenne's muscular dystrophy or severe haemophilia or who are at risk of being carriers of other deleterious X-linked genes
- couples at risk for detectable inborn errors of metabolism (for example, Tay-Sachs, mucopoly-

saccharidoses, that is, a group of disorders due to a defect in mucopolysaccharide metabolism)

- previous neural tube defects

Indications do not, however, solely reflect medical practice; they also reflect the rationale of individual and collective expectations about procreation and the quality of offspring. A letter in the *New England Journal of Medicine* illustrates this aspect of indications. Ms. Diana Paul described how she won a "battle with the bureaucracy and underwent amniocentesis at the age of 30," although she was not eligible according to the policy of the state of California. She said that "in view of the fact that every woman has the constitutional right to an abortion, it seems unreasonable to deny a woman the kind of information that she may believe is vital to her decision about whether or not to proceed with a pregnancy." In effect, the author goes on to say, "a physician who denies amniocentesis to a women who understands and assumes responsibility for any possible risks to her health is obstructing her right to abortion."[50]

Several professionals wrote to the *Journal* in reply to Ms. Paul's letter.[51] A genetic counsellor stated that it was apparent to her that the issue of "amnio before 35" was becoming a real and complex problem. She further argued that "35 years has traditionally been the cut-off point because it is the age at which the risk of miscarriage due to the amniocentesis has been equated to the possibility of the presence of an anomaly." This standard may no longer hold true. A physician also wrote that "people have rights to health and good medical care (including abortion when appropriate) but no one has a right to unnecessary medical care. Deciding what is necessary and unnecessary must be the province of both doctor and patient, and not of either one alone." Another health professional stated that "customarily, procedures are performed for indications, not at the whim of the patient."

All this correspondence revolves around one issue: Which group should have access to prenatal diagnosis? Who decides the question of accessibility – geneticists, counsellors, pregnant women, politicians?

Goals and Means in Prenatal Diagnosis

The medical goal. There is general consensus among geneticists that "the fundamental philosophy of prenatal genetic diagnosis is to reassure those at risk that they may selectively have unaffected children when the procreative risk for having defective children becomes unacceptably high."[52] It must be stated very clearly that in the great majority of cases (approximately 95 per cent), prenatal diagnosis confirms the presence of an unaffected fetus. For the remaining 5 per cent, the issue of selective abortion has to be faced, and, indeed, termination of pregnancy is chosen in almost all of such cases. This has led many people to believe that abortion is an essential part of prenatal diagnosis. A less absolute policy appears in this statement: "Ideal screening programmes would offer abortion of all severely affected fetuses while reducing to a minimum the risks to normal fetuses and allowing those with minor and remediable malformations to go to term."[53] All in all, it would seem correct to acknowledge that the medical aim of prenatal diagnosis is to detect affected fetuses and help people at risk to recover normal rates of fertility. In this manner, the burden of disease would not be placed on society.

As noted earlier in this chapter, however, the very fact that abortion seems to be linked with amniocentesis creates a major obstacle to the acceptance of genetic services. The major ethical issue associated with amniocentesis remains the issue of abortion itself.[54] Benzie, quoted earlier as seeing prevention and treatment, not abortion, as the aim of prenatal diagnosis, consistently opposes the detection of abnormalities, such as cleft palate, that are not lethal or that are often compatible with normal life.[55] Others point out that therapies will increase and offer an alternative to either abortion or living with an incurable disorder, and "measurements of skin and blood concentration of drugs will permit maintenance of therapeutic levels in the fetal patient."[56]

Fetal therapy is not highly developed in genetic medicine. Of the thousands of genetic diseases and the hundreds detectable before birth, only a handful can be treated. If one were to list the current state of treatment on the tables of disorders and their detection, the majority would read "no effective therapy is known"; and sometimes, as in the case of Tay-Sachs, it would be followed by the phrase "despite various efforts." Therapeutic power, indeed, lags far behind diagnostic power in genetic medicine.

In August 1981, a survey article on the management of the fetus with a correctable congenital defect reflected the state of the art, as shown in the following excerpt:

> **Management of Fetal Malformations**
>
> ***Managed by selective abortion***
>
> Anencephaly, porencephaly, encephalocele, and giant hydrocephalus

Severe anomalies associated with chromosomal abnormalities, *i.e.* trisomy 13, trisomy 18
Renal agenesis or bilateral polycystic kidney disease
Inherited chromosomal, metabolic, and hematologic abnormalities, *e.g.* hemoglobinopathies, Tay-Sachs disease

Detectable in utero but best corrected after delivery at term

Esophageal, duodenal, jejunoileal, and anorectal atresias
Meconium ileus (cystic fibrosis)
Enteric cysts and duplications
Small intact omphalocele
Small intact meningocele, myelomeningocele, and spina bifida
Unilateral multicystic dysplastic kidney
Craniofacial, extremity, and chest wall deformities
Cystic hygroma
Small sacrococcygeal teratoma
Ovarian cysts

May require induced preterm delivery for early correction ex utero

Obstructive hydronephosis
Obstructive hydrocephalus
Amniotic band malformation complex
Gastroschisis or ruptured omphalocele
Intestinal ischemia-necrosis secondary to such conditions as volvulus and meconium ileus
Hydrops fetalis
Intrauterine growth retardation

May require ceasarean delivery

Conjoined twins
Giant omphalocele, ruptured omphalocele/ gastroschisis
Large hydrocephalus
Large sacrococcygeal teratoma
Large cystic hygroma
Large or ruptured meningomyelocele
Malformations requiring preterm delivery in the presence of inadequate labor or fetal distress

May require treatment in utero

Deficiency states that may be alleviated
Deficient pulmonary surfactant (pulmonary immaturity)
Anemia-erythroblastosis and hydrops
Hypothyroidism and goiter
Methylmalonic acidemia (B_{12}-dependent)
Multiple carboxylase deficiency (biotin-dependent)
Nutritional deficiency and intrauterine growth retardation
Anatomic lesions that interfere with development
Bilateral hydronephrosis (urethral obstruction)
Diaphragmatic hernia
Obstructive hydrocephalus[57]

The prospects of prenatal treatment are, indeed, limited. A few diseases can be treated after delivery through diet, such as PKU and galactosemia (a disease that prevents the metabolism of sugar derived from lactose in milk). In the case of the latter, the mother's diet during pregnancy helps to avert the development of mental retardation. The same probably applies for deficiency of the liver enzyme called arginase and for maple-syrup urine disease. Often surgical and orthopedic interventions are the only possible correctives. For others, symptomatic treatments alleviate the disease. Prenatal treatment has, for example, been reported of "an autosomal recessive disorder, methylmalonic aciduria, which causes mental retardation, failure to grow, and life-threatening acidosis. It exists in several forms, two of which respond to treatment with large doses of vitamin B 12. At least one child with the disorder is now growing normally after prenatal diagnosis and prenatal treatment."[58]

Experimental fetal therapies, such as antenatal treatment of hydrocephalus and of congestive heart failure, are regularly being reported in the literature.[59] In the spring of 1981, Birnholz and Frigoletto mentioned early diagnosis of hydrocephalus and subsequent treatment by withdrawal of ventricular fluid through cephalocentesis.[60] This method is particularly important if hydrocephalus has been detected in the first 24 weeks of gestation, when it is too early for delivery and surgical decompression. In June 1981 the New Jersey-Rutgers Medical School reported a case of fetal tachycardia in which congestive heart failure developed in utero. At 26 weeks of gestation the problem was identified and treated by administration of drugs (digoxin) to the mother. In March 1982 a Yale Medical School team reported using echocardiography for evaluating in utero congestive heart failure in 13 fetuses. In three cases treatment was given: one responded to cardioversion at birth, another responded to transplacental digoxin therapy, and the third died before delivery.[61] In March 1982 the Fetal Treatment Program of the University of California at San Francisco also reported fetal surgery for congenital hydronephrosis, that is, accumulation of urine in the pelvis.[62]

The ultrasonic detection of fetal malformations in late pregnancy, that is by 20 to 25 weeks, creates a new situation for parents and obstetricians. Therapeutic choices increase. Other than terminating the pregnancy, one may consider advancing the delivery for earlier treatment, decompression of the fetal mass, ceasarean section, or intra-uterine therapy. So far, three malformations have been chosen for treatment in utero: obstruction of the urinary tract, hydrocephalus (water on the brain), and hydronephrosis. Of these, physicians currently consider the first to be the only suitable candidate for treatment in utero, although the experimental and clinical experience remains to be pursued for the other malformations. The Department of Obstetrics and Gynecology at the Health Sciences Center in Winnipeg is keeping an International Fetal Surgery Registry. As of July 1983, 30 cases of attempted treatment of hydronephrosis and 17 cases of attempted treatment of hydrocephalus had been reported.[63]

A final aspect of innovative and experimental treatment of the fetus is the conflict between the need for careful peer review and the public's right to know. The ethics of news reporting are particularly at stake. A case at the University of Colorado, Denver, illustrates this point. In April 1981 a multi-specialty team designed and implemented an experimental treatment for a 23-week-old fetus with congenital hydrocephalus secondary to X-linked aqueductal stenosis, whose parents had declined to terminate the pregnancy.[64] A local newspaper heard of the surgery and obtained an unpublished manuscript on the case, which it quoted extensively. When the medical team refused to comment, the newspaper filed a grievance report with the local Code of Cooperation Committee. This committee stated that the doctors were wrong in withholding information on a patient who, upon becoming a public figure, had given up her rights to privacy![65] Is the press free to disregard the patient's right to privacy and the investigators' right to release their story at the time and in the place of their own choosing?

Genetic screening. Complementing prenatal diagnosis are genetic screening programs. Ideally, these programs include advice, based on the results of the screening tests, about the reproductive options open to the counsellees. There are two main objectives of genetic screening. The first is identification of persons at risk for their own health and for whom early medical intervention can be beneficial. The best-known example is PKU screening, the detection of phenylketonuria in newborn children, followed by the earliest possible dietary control to reduce brain damage. Some countries have, since the early 1960s, been screening all newborns for PKU. At present more than 20 countries follow this procedure, and "there is no question that these programs have led to the prevention of mental retardation in hundreds of children."[66]

The second objective is identification of persons who have genes that, in specific combinations, may bring harm to their offspring and who, therefore, may benefit from counselling about reproductive options. One such program is the screening for sickle-cell anemia. Several American states launched a genetic screening program for the sickle-cell trait in about 1972, even though no techniques for treatment or prenatal diagnosis existed. These programs are designed to identify carriers for the sickle-cell trait. Carriers themselves do not have the disease (chronic hemolytic anemia); these persons lead normal, active lives. When two carriers mate, however, their children may have the disease. Many people were unaware of this vital distinction. "The trait was misrepresented as a health hazard leading to unnecessary anxiety and sometimes discrimination with respect to insurance premiums and eligibility for certain jobs."[67] Thus, the U.S. Air Force Academy in the late 1970s disqualified all candidates who were found to be sickle-cell trait carriers, and some black pilots were fired. Since then no causal relation has been established between the sickle-cell trait and collapse or sudden death under conditions of strenuous exercise. The Air Force Academy backed down in 1980 and agreed not to disqualify any otherwise eligible black applicant simply because of his or her status as a carrier of the sickle-cell gene. Even though there is evidence that environmental factors (lack of oxygen, higher altitude, or dehydration after physical exercise), trigger sickling of blood cells in some carriers, the sickle-cell trait itself does not cause the sickling.[68]

Determining the group to be screened and counselled depends upon the frequency and severity of the disease, upon the availability and efficacy of therapy, and, finally, on cost and benefit. Using these criteria, practitioners have identified three groups for screening: (1) the whole population, for PKU only; (2) the subgroup at risk of having affected offspring (for example, Blacks for sickle-cell anemia, Mediterranean races for the blood disease called bêta thalassemia, Ashkenazi Jews for Tay-Sachs disease, and pregnant women of advanced age for trisomies); and (3) any family with cases of hemophilia, Duchenne's muscular dystrophy, Tay-Sachs, neurofibromatosis, tuberous sclerosis, or when the counsellees are themselves affected (early coronary artery disease, peptic ulcer, G6PD deficiency).[69]

Among the better and more successful screening programs within the field of genetic counselling and prenatal diagnosis is Tay-Sachs screening in the United States and thalassemia screening in the Cypriot community in London, England. Dr. Michael Kaback, professor of pediatrics at the University of California at Los Angeles, testified to a presidential commission:

> Approximately 350 000 Jewish young adults have been screened voluntarily. Nearly 15 000 heterozygotes [that is, "carriers"] have been identified, and 288 couples have been identified as being carrier-carrier marriages. Each child born into such a marriage is a one in four risk of manifesting Tay-Sachs disease. Pregnancies that are "at risk" can be screened through . . . amniocentesis.[70]

The International Symposium on Recent Advances in Thalassemia, June 1981, heard of the London Cypriot community's reaction to the availability of prenatal diagnosis.[71] Modell stated that during the previous two years, not one single case of bêta thalassemia has been reported. An earlier study on the Cypriot community illustrated the many difficulties in conveying accurate counselling to a whole community and the need for active involvement of all health workers, especially general practitioners.[72]

In Canada, the major emphasis of government programs is on hereditary metabolic disease. Relatively little effort has yet been invested in other genetic diseases, such as chromosomal or multifactorial diseases.[73] It should be mentioned, however, that in 1975 a study on genetic screening programs, undertaken by the U.S. National Academy of Sciences, described the Canadian PKU screening programs and practices as being ahead of those in the United States.[74]

In the Province of Quebec, genetic screening focuses primarily on PKU, hypothyroidia, and tyrosinemia. A special program exists for Tay-Sachs screening among Ashkenazi Jews and one community of French Canadians. From 1969 to 1985, the PKU screening was expected to save $31 795 589.15 in state expenses, $913 971.95 in cumulative national savings, and $227 723.30 in family savings. These estimates were made against treatment costs of $696 890.95 during the same period.[75]

Decision Making and the Future of Genetic Screening

Concerns about the directions and trends in genetic screening programs have been raised regularly. F.A. Isambert, a French sociologist, notes the danger of making patients less autonomous, as well as that of making serious decisions banal. When amniocentesis is performed automatically in cases of risk, and when abortion becomes the thing to be done for severe fetal deformity, doctors and patients are alienated from their responsibility.[76] The temptation grows, especially in mass screening programs, to leave medical decisions to the dictates of laws and rules rather than to the personal judgment of physicians and patients in the private sector.

S.J. Reiser also opposes this trend and believes that we ought to look for a principle upon which to decide the question of screening for genetic diseases. Already, from the viewpoint of cost and risk, it is evident that we "cannot do everything diagnostic medicine is capable of doing. In the absence of such a precept, we allow combinations of random social, scientific and political events to determine which tests become compulsory."[77] Reiser opposes the legal and quasi-legal rules that make physicians follow certain patterns of diagnosis. He supports instead, the prescription of diagnostic tests on the basis of the doctor's clinical judgment.

If policy makers believe that prenatal diagnosis is a matter of wide public concern and that it should not be left solely to the competence of patients and doctors, they will then have to look for guidance. Those who disagree with using random social, scientific, and political events as criteria for screening will face the difficult task of determining which criteria should be decisive.

The goals of prenatal diagnosis as declared and professed by those asking for it and by those offering it are not always clear. These people mention procreation of healthy offspring, reduction or even prevention of incidence of illness, positive and negative eugenics. Moreover, it is not clear who sets these goals. Is it those who control the means to achieve them?

Are goals and priorities determined by a mutual reinforcement of medical technology and social expectations? Each of these phenomena receives much attention from the media. Should more attention be given to alternative goals and means? Consider the possibility of limiting the procreative choices of couples at risk by either absolute or relative restrictions. And what about the consistency between ends and means? It is one thing to affirm in theory the policy maker's responsibility to protect the values of individual citizens, yet to promote simultaneously the maximum benefit for society. It is quite another thing to harmonize much-needed screening programs with adequate care for those already living with the disease.

Prenatal Diagnosis in Canada

Genetic programs in Canada have emphasized hereditary metabolic disease, but to cope with the full spectrum of genetically influenced disease, a much wider effort is necessary. Overviews of the Canadian experience, particularly of the Quebec Network for Genetic Medicine, have repeatedly insisted on the need both to expand laboratory facilities and to increase the number of trained personnel.[78] In a time of scarce resources, it will be difficult, however, to meet the growing public awareness of and the rising demand for genetic services.

A 1980 survey of four centres operating in Montreal, Toronto, Winnipeg, and Vancouver revealed a unanimous complaint about the critical shortage of personnel and space needed to further genetic programs.[79] The shortage places a chronic burden on people operating beyond capacity in a service where no one can afford to lower the quality of performance, let alone make mistakes. The co-ordination of medical, technical, and laboratory facilities is essential to the quality of genetic centres.

The reports of the four centres showed unanimous concern for the socio-economic status of women seeking prenatal diagnosis. It was found that the greater the income and education, the more likely the woman is to seek prenatal diagnosis. This was particularly true in the group aged 35 to 39. Since prenatal diagnosis is available, in principle, to all women, and since it is covered by provincial health-care systems, the current limitation on access to genetic services is an issue for research and possibly for future action, information, and education.

The Winnipeg report contends that genetic services are distributed unevenly in Manitoba. Although 60 per cent of the women of that province over the age of 35 live outside of Winnipeg, 85 per cent of referrals were from Winnipeg and only 15 per cent from other parts of Manitoba. Another study, made in Ontario, confirms the impression that city people are more aware of genetic medicine than are rural people. When researchers compared a large hospital in a city of 250 000 with a small community hospital in a city of 25 000, they found that the smaller hospital discharged a greater percentage of children with genetic disorders.[80] Most of the 20 or so genetics centres in Canada are in cities with a population of more than 250 000. It seems reasonable to conclude that women in cities have fewer children with genetic disorders because they either are treated or have abortions.

The Manitoba and Quebec reports, expressed great concern that genetic services were not yet widely accessible to the population. Underutilization of these services in rural areas stems from lack of knowledge of the availability of the services and the proper indications for their uses, rather than from a rejection of the procedures.

Canadian abortion laws differ from those of the United States and the United Kingdom.[81] Canadian law does not admit eugenic indication for the termination of pregnancy; that is, it is illegal for a woman to have an abortion because the fetus has a genetic defect. The only exception occurs when a therapeutic abortion committee certifies that continuation of a pregnancy would be likely to endanger the mother's life or health.

In 1975 the Canadian College of Medical Geneticists was formed to establish and maintain standards of quality in medical genetics services. Admission to the college is by examination, and the college has set criteria for the training of medical geneticists; it has also set standards of quality for medical genetics centres, which it evaluates. To ensure a smooth and constant flow of service, provincial health authorities assume responsibility for the organization, division, respective fields of specialization, and common back-up systems. In some provinces genetics services are organized by providing funds to a network. In certain cases, these networks must collaborate with governmental authorities for the actual distribution of services and the establishment of centres throughout the province.

The report "Diagnostic prénatal au Québec 1980" illustrates this collaboration between the Réseau provincial de médecine génétique and the ministère des affaires sociales (that is, the Quebec Health Ministry). The major points of this report are the recommendations for creation of a third centre for genetics services in the province and the provision of immediate accessibility to genetics services to every woman over the age of 40 and, within a few years, to all women over 35.

Meanwhile, existing centres throughout Canada are trying to keep up with the rapid growth in demand for services and with future developments. This struggle to cope must not prevent them from building consistently so that internal and local policies may conform to provincial and national policies.

With so much good will and devotion on the part of geneticists, it would seem reasonable for health ministries to delegate to provincial networks the authority to run genetics services. It would be demoralizing for geneticists to see themselves as bearing a great deal of responsibility but possessing no authority.

Dr. Patricia Baird's look at the future development of the Vancouver program of prenatal diagnosis probably describes the views of many Canadian geneticists:

> This field is obviously expanding at an unprecedented rate. The demand on the part of the public for testing which will detect genetic abnormalities appears to be one which realistically will increase very quickly. With today's small families it seems that parents want to ensure as much as they can, that the children they do have are as perfect as possible. It has been shown in various studies that the procedure seems to be cost-effective for the diagnosis of chromosomal problems down to a maternal age in the early thirties and it is likely this indication will be increasingly used. As advances occur in the basic science aspects of genetics, more and more genetic disorders will become detectable.
>
> With mapping of the human genome taking place at a rapid rate, it is likely that gene markers will be found which means we will be able to detect very many disorders even if we cannot detect the actual gene product. This means that it will be necessary for society and government to do some concentrated thinking and make an evaluation of how much of society's resources should be put into a prenatal diagnosis program. I would see that program expanding rapidly, not only in terms of the numbers of eligible couples reached using our present indications, but by an increase in the number of indications as well. One of the limiting factors on this expansion will be the amount of funding allocated by government to it. This allocation obviously will be affected by the way society and parents in general see the priorities.[82]

Perspectives, Trends, Values

A wide variety of viewpoints, competing trends, and values constitute the multicoloured backdrop for the stage of genetic medicine. It would be a mistake to look for answers by drawing on only one of these. Neither cost effectiveness, nor statements of principle, nor any other single standard will provide a satisfactory public policy.

Current Choices

Some couples at risk do not want to remain childless, nor do they wish to adopt. They rely on prenatal diagnosis in order to produce unaffected children selectively. Their request triggers a complex mechanism with many more hidden choices and implications; for example, these couples add to society's trend to abort defective fetuses. Thus, while specific instances of genetic planning seem obvious, the trend is not always clear.

For most people amniocentesis offers one of the following outcomes: if the result is negative, continue the pregnancy; if the result is positive, terminate the pregnancy, or continue the pregnancy and treat if treatment is available, or continue the pregnancy without treatment.

It is sometimes argued, especially by those who oppose prenatal diagnosis, that geneticists and clients alike consider only the first two possibilities. This may be a misrepresentation of the facts. It is true that in 95 per cent of amniocenteses the result is negative, and, therefore, the pregnancy continues. It is also true that in the remaining 5 per cent, where the result is positive, the majority (more than 90 per cent) choose termination. Nevertheless, where treatment exists, as for galactosemia, many physicians who perform prenatal diagnosis assume that a patient will continue her pregnancy. To these physicians abortion would not be an equally appropriate alternative. It may be assumed, therefore, that as treatment possibilities increase either in utero or at birth, termination of pregnancy would be less frequently chosen, if it were available at all. Moreover, one hears about cases where a positive result confirms that the fetus has Down's syndrome, yet women decide against abortion. Similarly, 15 per cent of women at risk of bearing a child with sickle-cell disease and having obtained a positive test result nevertheless refuse abortion. In sum, all the outcomes mentioned above are realistic possibilities.

Prenatal Diagnosis and Abortion

Elective abortion very often means late abortion, well into the second trimester of pregnancy. Many hospitals set 20 weeks of gestational age as the upper limit, and a few hospitals in the United States permit elective abortions as late as the twenty-fourth week. Among the most likely possible complications in late abortion are septic infection, post-abortion uterine bleeding, and trauma to the cervix.

The most widely accepted method of second-trimester termination of pregnancy is intra-amniotic instillation of either prostaglandins (a substance that stimulates muscle contractions) or hypertonic saline. Administration of prostaglandins has some side effects, but few serious complications. Saline instillations, however, have several possible serious complications. Current methods are not ideal, from the standpoint of effectiveness, safety, and the ability to confirm the diagnosis in the products of conception. Confirmation of diagnosis is imperiled because of the damage saline instillation causes in fetal cells.[83]

The relatively high incidence of psychological sequelae is also of concern to doctors, who emphasize the need for thorough counselling before prenatal diagnosis and especially before abortion. They recognize that the contradictory experience of wanting to become pregnant and then terminating the pregnancy because of a fetal defect is potentially traumatic and pathogenic. The striking difference between abortion because of a fetal defect and early termination for social indications, that is, because the pregnancy was unplanned or unwanted, is that the latter is rarely accompanied by severe or persistent psychological or adverse social sequelae.[84] Others point out that depression occurs more often, lasts longer, and affects both husband and wife when there is genetic termination of pregnancy.[85] Therefore, some genetics services now provide psychological support before termination to alleviate the major trauma of the sudden loss of a highly desired being.[86]

Finally, there are legal complications. In Canada, for instance, a female's pregnancy may be terminated only "when continuation of the pregnancy . . . would or would be likely to endanger her life or health."[87] In any particular case, however, the mental health criteria for therapeutic abortion may be satisfied after a woman learns of gross fetal abnormality.[88] Another legal complication derives from the lateness of these abortions. Even in countries with more liberal abortion laws, such as the United States, doctors are generally reluctant to perform late abortions. There, however, "it seems settled that an adult woman has an unqualified right to obtain an abortion during the first trimester of pregnancy, a right to obtain an abortion up to the time of fetal viability under conditions reasonably intended to protect her, and, a qualified right to terminate her pregnancy after the fetus has become viable when her life or health is threatened by the pregnancy."[89]

Future Generations and Gene Frequencies

What of the woman who wants to bear children even though she is found to be a 21-21 translocation carrier, which means she will produce mongolism in all viable offspring? Or, what of PKU patients and children with neural tube defects who are successfully treated and live on to reproductive age? Is it unthinkable, and, if so, will it remain unthinkable, for genetic counsellors or society to request such people to abstain from procreation? Yet some of the causes of increased deleterious genes lie with medicine itself. Nora and Fraser have stated that "medical advances have improved the fertility of patients with many hereditary diseases. Will we thereby become a species of malformed morons?"[90] They went on to observe that "medical care is dysgenic (having a detrimental effect on hereditary qualities) and, in the absence of countermeasures, will lead to an increase in the frequency of genetic disease. Will the increase be large enough to cause concern?"[91]

These provocative questions reflect the area of gene frequencies in populations, that is, the proportion of advantageous versus deleterious genes in the genetic pool. Medical advances are, of course, only a recent addition to the factors that influence the equilibrium of genes. Major factors always at work are mutation and selection: mutation by adding new alleles, and selection by reducing or increasing the gene frequencies. Environmental factors are also at work.

The measurement of gene frequencies and their changes is of interest to parents "who want their children to be free of genetic disease." It is also of interest to health policy makers and others who are "concerned with forecasting the need for health care facilities" and "will want to know ahead of time."[92]

The literature on the effects of technology on gene frequency and disease frequency is rapidly growing.[93] Its conclusions, however, appear to be neither final nor unanimous. Practical and particular policies will have to be established ad hoc and according to local priorities.

What worries most geneticists is not a possible increase in the frequency of lethal diseases recessively inherited. To increase this frequency from one in 10 000 to one in 2500 would take 100 generations. What does worry geneticists is the cumulative effect on gene frequencies as more diseases become treatable and "natural" selection is relaxed. This effect would be greater for dominant than for recessive traits. Finally, for diseases with multifactorial etiology, such as myelomeningocele, survival of a successfully treated patient to reproductive age would increase the disease by 3 per cent per generation. "Prenatal diagnosis will be a counter-balancing influence in this case."[94]

It may be possible to protect future generations against the dysgenic effects of relaxed selection if society is willing to practise negative eugenics. This means that harmful mutant genes are reduced through a program combining prenatal diagnosis and selective termination of pregnancy. Since eugenics (especially positive eugenics, which will increase the frequency of beneficial genes) always raises the spectre of abuse by authoritarian, racist regimes, it may be well to recall the hopes of geneticists that "any program for reducing the frequencies of deleterious genes would be by education and voluntary co-operation, not by any form of coercion."[95]

Whose Cost and Whose Benefit?

Cost-benefit and cost effectiveness of both the economic aspects and the human values involved in prenatal diagnosis are a major concern to decision makers. Neither type of calculation is clear and easy, however, since it relies, implicitly or explicitly, on assumptions and evaluations that resist quantification. As one commentator has observed, "In general, one should be quite skeptical of such analyses and a full consideration of other than economic benefits in planning new programs should always be carried out."[96] Nevertheless, efforts at economic analysis have been made and are likely to be of some help.

Authors of one study calculated that for the prevention of Down's syndrome, the potential monetary benefits would be greater than the costs for women over the age of 40, about equal to the costs for those aged 35 to 39, and less than the costs if the service were extended to women under 35.[97]

In a study of cost-benefit ratios for spina bifida screening programs, the same authors concluded that cost effectiveness would apply only in a population with a high incidence of spina bifida.[98] Others, however, advocate early treatment of infants with spina bifida as most cost efficient.[99] Still others predicted that an AFP-screening program for England and Wales would more than pay for itself within five years from savings in cost of the care of affected children.[100] In the United States, Layde and colleagues pursued the calculation of a similar AFP program for spina bifida and emphatically stated that "the total cost of the program to screen 100,000 such women was calculated to be $2,047,780 or slightly over $20 per woman screened, while the total economic benefits exceeded $4,000,000."[101] According to the authors, the favourable cost-benefit relationship gives the ethical debate added meaning because the technical and economic feasibility of screening now puts the onus on the outcome of the ethical debate.

Many analysts are aware of the difficulty in measuring such intangibles as parental distress, parental devotion, breakdown of the marital relationship, the quality of the life of affected children, and the loss of an unaffected fetus. The last possibility, for instance, would be unacceptable for some, no matter what economic benefit to society might be derived from it, whereas others would see lost pregnancies as easily replaceable.

Cost effectiveness remains a tool for decision making. Quite understandably, policy makers also rely first and foremost, although not exclusively, on economic analyses.

Genetic Registration

Since the banking of information, including areas of medicine and health care, is becoming a major need of our society, the processing of such data has raised several very sensitive issues. One of the frightening scenarios, perhaps unfounded at present, is that of a Big Brother manipulating genetic records and, consequently, steering individuals or groups away from certain career opportunities. This potential threat to privacy and freedom has been widely publicized. Speaking of the use of computers, the Royal College of Physicians in the United Kingdom stated concerning the use of computers, that "there is a need for an agreed and consistent code of practice amongst the medical profession as a whole."[102] Should such codes of practice subsequently become legally enforceable? Or should the guarantee of confidentiality depend on the integrity of the doctor running the computer system? Or should there be safeguards in the system itself?

Questions of confidentiality arise most acutely with multidisciplinary teams sharing research and computers.[103] In genetics the counselling team, the urgency of research, and the new need for genetic registration with computers seem to have brought this issue to a head. So far, confidentiality and respect for privacy seem to have prevailed in the genetic registry systems. This may reflect the public's value choice of today, but not necessarily the professionals' preference.

The policy question prompted the *Lancet* editorialist to ask, "But is the public ready for wide deployment of genetic registers?" He also recommends that we "continue to seek other and less controversial methods of transmitting information of genetic risks to all those who need it."[104]

Conclusions

Policy makers face the difficult task of guiding the practice of prenatal diagnosis, its programs, and their accessibility in a direction that is beneficial to individuals and to society. Monetary considerations, people's expectations and preferences, as well as their prejudices, are all important factors. To reach a policy decision, however, it will be necessary to compare options and to determine priorities. The final section of this chapter summarizes the policy issues and focuses briefly on other related issues of interest to the policy maker.

Issues for Public Policy

It must be borne in mind that prenatal diagnosis is a rapidly evolving technique in a field where services have increased 50-fold within 10 years. Furthermore, there is no reason to expect less demand for these services in the future. Genetic medicine is so crucial to society that it should not be left in the hands of geneticists alone. Rather than wait for the 95 per cent of human genes to be mapped in the very near future, a process that would allow little time to pause and think, society must face the issues now and thus attain a position from which to deal with future questions.

The following list does not attempt to classify these public policy issues by importance, effect, urgency, imminence, newness, or by any other criterion. (On some of these issues it will be useful to consult earlier sections of this chapter, where they have already been treated.) The following topics merit further study:

- amniocentesis
- maternal age
- genetic screening for carriers
- genetic registers
- insurance industry and genetic disease
- research
- cost effectiveness
- fetal therapy
- sex determination and pre-selection
- "wrongful life" cases
- introduction of new technologies
- self-control or public control of professionals

Amniocentesis

In addition to encouraging the wide application of genetic amniocentesis, the International Workshop on Prenatal Diagnosis at Val David identifies the following new needs:[105]

- basic work on the origin of cells in amniotic fluid
- more rapid techniques for culturing amniotic cells
- more non-invasive screening techniques, since not all women support amniocentesis
- follow-up of amniocentesis patients and their babies to examine the effect of the test on their lives

There is still no conclusion on the debate about potential physical harm to the fetus through amniocentesis. The British reports mention slightly increased risks of fetal loss or later complications. The American and Canadian reports found no significant increase in risk. The medical profession must be encouraged to clarify this issue.

In addition to the assessment of physical effects of amniocentesis on babies, we need studies on what influence, if any, this test may have on infant behaviour and development. In a current Toronto project, which may offer valuable insights into the matter, researchers will evaluate children at three days of age, six months, and when they reach seven years.

Maternal Age

Indications for amniocentesis generally include pregnant women aged 35 and older. As noted in a preceding section cost effective prevention of Down's syndrome is for women aged 35 and older.

Another rationale is that 35 used to be the age where the risk of miscarriage occurring as a result of amniocentesis was equated with the possibility of the presence of an anomaly. But what happens when these "equations" change? What happens, that is, when the risk of miscarriage is likely to be much smaller, or when the difference in risk of chromosomal anomaly occurring at age 30 (1:400) is no longer considered to be statistically significant compared with the risk at age 35 (1:200)? In any case, is it reasonable to equate the risk of an abortion with the risk of having a Down's syndrome child with all the psychological and economic costs involved?

Has the time come, then, when the old standard of risk being equal at age 35 no longer holds true? As long as women understand the risks involved, should they have access, whenever possible, to any procedure that could significantly alter the future of their families?

Can it be argued that a woman's constitutional right to abortion (as it stands in United States) also gives her the right to information that may be vital to her decision whether to proceed with her pregnancy? Consequently, has a physician the affirmative duty to increase access to amniocentesis? Or should policy or law limit access to amniocentesis to women with medical indications? Indeed, to employ a specific maternal age as a cut-off line is a matter not only of resources but also of philosophy.

Genetic Screening for Carriers

Genetic screening is here understood as the search for persons possessing genotypes that may lead to disease in their descendants. These persons are not sick themselves, but are carriers. To define them as "couples-at-risk" when both partners are heterozygous carriers will enable them to prevent defective offspring by using prenatal diagnosis.

So far, the major screening programs for carrier detection have been for sickle-cell anemia in Blacks and for Tay-Sachs disease in the Jewish population in the United States, and for thalassemia in the Greek Cypriot community in Britain. Success seems to depend on four conditions: (1) high levels of motivation, (2) knowledge, (3) availability and acceptance of prenatal diagnosis, and (4) cohesiveness in the community. As the *Lancet* editorialist concludes, however, "It remains true that no screening programme for carriers of any genetic disorder in an entire population (as opposed to high-risk sub-group) has yet been shown to be effective."[106]

The same editorial states that the timing of screening is perhaps the most crucial decision to be made for each disease. With cystic fibrosis, for example, the question is, when should screening take place? At birth, possibly in combination with PKU tests? During childhood, or when formal schooling terminates? Or after pregnancy has started, possibly along with AFP testing in the antenatal clinic? Indeed, every condition is different and requires its own approach. There is no across-the-board approach to genetic disease.

Genetic Registers

The establishment of genetic registers has been a controversial issue since the early 1970s. The need for genetic knowledge makes broader access to information about one's family essential. Some family members may be affected by genetic disease and could, therefore, be expected to be in favour of registration; others, affected or not, could feel quite differently.

To ascertain and prevent genetic disease, the establishment of a genetic register seems to be justified. In centres of genetic study in Edinburgh, as well as in many other European and North American cities, efforts have been made to reconcile this need for knowledge with the values of privacy and confidentiality.

In a report on the ethics of genetics counselling, a commission of the Health Council of the Netherlands supported the view that only a central registry system could provide information about the frequency, incidence and potential causes of genetic disorders.[107] The commission favoured anonymous over full-name registers, to protect individual privacy. Yet, genetic diseases by their very nature often cannot be fully diagnosed without information on other family members, dead or alive, obtained through the history of a patient and his family. In this respect, having access to the files of a patient becomes essential. Furthermore, currently computerized information may become of vital interest only after many years. By then, anonymous data would be of little help.

In the not-so-rare cases of balanced chromosomal translocation, a patient can be helped only if the family and the family doctor are told about the condition. At an appropriate time, such as when children marry, the family doctor brings the family's problem of hereditary disease forward again and counselling can be offered. A genetic register may be most significant for the dominant diseases of adult onset, such as Huntington's chorea, again, on condition that either the family or the family doctor is aware of the family history. This sharing of medical histories violates, however, the obligations of confidentiality and respect for privacy.

In 1978 a working party of the Clinical Genetics Society in the United Kingdom recommended the following:

- Registers should be set up to help geneticists trace and counsel persons at high risk of transmitting a serious genetic disorder. Such registers are already kept by units concerned with special disorders such as hemophilia.
- Entries to the register should be made only with the full knowledge and approval of the person concerned.
- Regional centres should standardize their methods of recording data.
- Strict safeguards for confidentiality must be incorporated, with personal medical information accessible only to the consultant in charge of the register.
- A dedicated mini-computer in the regional medical genetics centre would provide the most convenient

method of ensuring ease of operation and confidentiality.

- A start should be made to register specific genetic disorders of particular importance.[108]

The Insurance Industry and Genetic Disease

Economic and financial factors complicate the management of genetic disease. Regardless of the health insurance system, the burden can be measured, if not by its effect on the family, certainly by its effect on the government through the health insurance industry.[109]

With the advent of genetic markers, the question of individual responsibility for health risk may be stated differently. Genetic markers are direct products of genes that forecast the likelihood of a specific disease. They will, therefore, play an important role in the insurance industry where "predicting life expectancy and illness—and determining insurance rates on the basis of those predictions—is the key to that industry's success."[110] Several such markers for allergies and for cardiovascular disease are already known. Genetic markers for the major histocompatibility complex already number nearly 100.[111]

Insurance companies will surely take greater interest in genetic information. Should these companies be allowed "to extend their mandatory physical examination to include genetic screening?"[112] Some persons will wonder why society should be forced to foot the bills for someone who knows he or she is at risk, yet persists in taking chances. Even in systems of socialized insurance plans, the same question will be raised: Should everybody be offered the same insurance rates, no matter what the risk?

Research

If it should be demonstrated that people want therapy, not prevention, then a drastic reordering of research priorities must take place. In any event, some experimental therapies are already very important, such as intra-uterine decompression of hydrocephalus, early decompression of the obstructed fetal urinary tract, the techniques of drainage of urine from the bladder into the amniotic fluid, and the correction of diaphragmatic hernia.

Meanwhile, priorities among geneticists seem to lie in research on genetic disease and their diagnosis. The 1979 International Workshop at Val David reflects this priority, as follows:

- Chromosome disease will require international collaboration and pooling of data for such topics as age risk and recurrence. Geneticists shall also need to develop a nomogram, that is, a value scale, delineating risk assessment, with special emphasis on the pregnancies of possible "high risk" younger couples. They shall need research on optional methods to amniocentesis and on measurement of possible exposure of the fetus to environmental agents.
- Neural tube defects will focus chiefly on AFP and ACHE, as well as on the incidence of chromosomal abnormalities in fluid taken after high levels of AFP.
- Indirect or linkage analysis of metabolic disorders will require attention be paid to the uncertainties affecting prediction of fetal genotype when the polymorphic markers, which are detectable prenatally, are only loosely linked to the defective gene. Methods of direct DNA analysis and linkage analysis must be developed, such as the method successfully applied in the use of HLA-B typing for the prenatal prediction of congenital kidney deformity.

Although prenatal diagnosis does not necessarily exclude the possibility of follow-up treatment of the diseased fetus, research priorities are mainly geared to diagnosis of the genetic disease. The emphasis is on the prevention of the birth of diseased infants and not on treatment, since diagnosis is now practicable and treatment is not.

Cost Effectiveness

Cost effectiveness and cost-benefit analysis are notoriously difficult when applied to the management of medical and health care services. There is also no conclusive evidence, on the cost effectiveness of prenatal diagnostic programs, although some practices do diminish the cost and increase the returns. These include:

- carrier detection, family history and, if indicated, amniocentesis for Tay-Sachs disease among Ashkenazi Jews and sickle-cell anemia among Blacks
- education and counselling
- genetic registration through family histories. (The moment government takes on the role of recordkeeping, however, the attractiveness is dimmed by considerations of cost and enforcement of confidentiality.)

- research: basic research guided by peer review, applied research guided by scientists and policy analysts, and policy research guided by participants in the policy-making process
- quality control and judicial policy (Governments assisted by courts ought to ensure the quality of prenatal diagnostic services.)[113]

Fetal Therapy

Fetal therapy is good news. Or is it? An article in the *Journal of the American Medical Association*, announced that "the fetus with a treatable birth defect is on the threshold of becoming a patient."[114] Yet another article in the issue attempted to temper this enthusiasm. In fact, it was argued, geneticists are creating just another set of hard choices for parents to debate and for mothers to consent to if therapy is to be performed through their body. The author then advocated the creation of as many choices as possible in order to learn as much as possible, and stay within legal guidelines on abortion.[115] Some would label this view as cool, cynical public policy.

Fetal therapy does, however, raise two major issues for public concern. First, what are the risks and benefits for both the fetus and the mother? How does one weigh, for example, the risks of intervention against the burden of malformation? Second, what is the moral, legal, and social status of the fetus? What are the rights of the mother and the fetus as patients?[116]

Sex Determination and Pre-selection

The detection of certain X-linked diseases cannot be done directly, but only through the determination of fetal sex. A mother carrying the hemophilia gene will have daughters unaffected by the disease, although each of them has a 50/50 chance of being a carrier. Each of her sons, however, has a 50/50 chance of being a hemophiliac. Since amniocentesis can determine fetal sex, these parents would have information to decide whether to continue or to terminate the pregnancy.

The International Workshop at Val David acknowledged that these X-linked diseases justified determining the sex of the fetus, so that parents could choose whether to terminate the pregnancy if the fetus were male.[117] Determination of fetal sex for social reasons alone, however, should not be considered a medical reason or an indication for antenatal diagnosis. Similarly, the Genetics Research Group of the Hastings Center strongly opposes movements "making diagnosis of sex and selective abortion a part of ordinary medical practice and family planning."[118] A debate in the *New England Journal of Medicine* reveals the influence of legalized abortion on demand upon the right to request sex determination for social reasons.[119]

The Wrongful Life Cases

Several cases of plaintiffs seeking damages for "wrongful life" have been reported in the United States. The New York courts denied the validity of such claims, but a California court acknowledged the trend to recognize the birth of a defective child resulting from negligence by others as a valid claim for recovery. In the Curlender case, where a child was born with Tay-Sachs disease, the court stated that "the reality of the wrongful life concept is that such a plaintif both exists and suffers due to the negligence of others."[120]

The same court dove into muddier waters when it logically extended the right of children to sue physicians for negligence to their right to sue their own parents for allowing them to have been born, especially if the parents had been properly warned. From a societal and ethical viewpoint, however, one must prove the underlying assumption, that is, the right to be born physically and mentally sound. Finally, the Curlender case may raise the possibility of a woman having a duty to abort her defective fetus.

The Introduction of New Technologies

The following recommendation was made at the International Workshop at Val David and deserves the attention of policy makers:

> When a new technology appears to be on the verge of widespread use, a consensus conference should be convened. Such a conference should be of a relatively small size and should include local experts in the field, outside experts, individuals from health disciplines, lawyers, persons concerned with the ethical aspects and representatives of agencies with fiscal responsibility for the development of service. Such a conference should be (1) charged with evaluation of the need for the new technology and whether the time is appropriate for its introduction; (2) evaluating the implications of widespread introduction into the population and (3) determining the current status of the technology elsewhere.[121]

An example of the development of a consensus is the evaluation of alpha-fetoprotein technology. It may be recalled that the assessment demonstrates how the combination of different techniques – in this case sonography, amniocentesis, and AFP – increases the risk and burden. Thus, there may be more unintended fetal loss, and the psychological stress on patients with a false-positive test is higher: "About 25 mothers would have to undergo this stress for each fetus with NTD that is aborted."[122] The panel's conclusion about such assessment was that "maternal serum AFP screening of all pregnant women should not be advocated at this time."[123]

In 1973 Amitai Etzioni had already launched the idea of a Council of Sages as the institutionalized answer to all the varied and complex questions raised by the introduction of amniocentesis and genetic engineering.[124] Such a council would inform policy makers, geneticists, and parents, but the ultimate decision would still continue to rest with the individual. It is to be expected that informed citizens will participate in shaping technocracy. Etzioni concludes, "As war is too important to be left to the generals, our bodies are too vital to be left to genetic engineers and doctors."

The Val David workshop recommended the creation of an "ombudsgroup" to ensure public involvement in genetic decision making. This group would have the functions of arbitration, negotiation, solution seeking, moral persuasion, and regular reporting. Moreover, it would play a role of ongoing policy evaluation, policy recommendation, balancing of competing needs and claims, funding, research, and service matters. The members of this ombudsgroup would be chosen from government, scientific and medical specialities, interest groups, and the general public.[125]

Self-Control or Public Control of Professionals?

Y.E. Hsia, an authority in the field of genetics, made the following claims of professional self-control:

- I know what I am doing. The law should leave me alone to do what I know is right.
- I know what is best for others. There ought to be a law to make everyone else do what I think is right for him or her.
- I know what needs to be done. There should be ample financial support for what I want to do.
- I know that what I have done was worthwhile. Everyone should trust me and respect my

> accomplishments, without demanding that I take the time to make detailed reports.
>
> - If anything has gone wrong, it is not my fault. The law should certainly recompense the unfortunate victims but not bother me.
>
> What I am doing is important – at least to myself.[126]

Hsia made these claims only partially with tongue in cheek, and he probably speaks for many of his colleagues. A lawyer, however, replied that government is becoming steadily more involved in the business of "modern eugenics," that is, trying, either directly or indirectly, to reduce the number of pregnancies that risk severe genetic diseases in the offspring.

It seems fitting to conclude by quoting a report to the U.S. House of Representatives: "Decisions on how society will handle its genetic disease carriers and genetically defective fetuses and neonates may, of necessity, become legal considerations."[127]

Chapter 3:

Genetic Engineering and Genetic Therapy

David J. Roy

> Nothing since the early days of atomic weaponry has caused so much dismay as the real or imagined threats associated with the development of genetical engineering and recombinant DNA research.[1]

Introduction

Many people today, among them scientists and specialists in genetics, are concerned that the development and future exercise of the powers emerging from recent progress in molecular biology and genetic engineering will be tantamount to "playing God." The fear is that science may advance to a nearly total understanding of the genetic blueprints of human life and spawn the technologies to manipulate and modify uniquely human characteristics. The prospect that human nature, taken for centuries as the norm of the common good and the public purpose, could be reduced to the status of a technological project has generated anxiety and dismay.

Others, including leading thinkers who are not scientists, have emphasized that recombinant DNA technology has rejuvenated molecular biology and permitted the design of industrial, pharmaceutical and medical projects that promise great benefit to all. The nascent ability to master the genetic correlates of disease may well lead to a profound transformation of medical theory and practice, perhaps eventually to the eradication or attenuation of diseases that cause untold human suffering. A realization of these trends would undoubtedly contribute to the advancement of the common good. What is most feared within this perspective is that visions of possible distant mischief could be used to block or seriously hamper highly promising initiatives in one of the most flourishing areas of contemporary science.

Many scientists are governed by priorities very different from the values that rule and the anxieties that perturb many other people. Those in charge of public policy can, for the sake of the common good and the public purpose, ill afford to ignore these differences. If long-term anxieties are successfully classified and brushed aside as merely "popular," "unscientific," and, therefore, "insignificant," a needed check and balance on the short-term goals of scientists, passionately interested in the advancement of their own work, may be seriously weakened and lost. Conversely, if long-term anxieties and images of distant mischief are collapsed into immediate threats, the risks of heavy, uninformed bureaucratic constraints on science and the advancement of the common good run high.

The advancement of the common good is precisely the issue. Few critical and informed persons today could immediately equate every scientific and technological advance with an advancement of the common good. Technological power is too ambivalent for that. The prospective development of engineering powers over the genetic correlates of human life unleashes fears that human genes and human beings will be reduced to engineering material. Some may ask whether there really is anything distinctively human about genes. That question is perturbing because, while human beings are dependent upon their genes, it is extremely difficult analytically to define what "distinctively human" really means. Will "distinctively human" be increasingly reduced to the shrinking domain of features that have not yet been scientifically understood and that cannot yet be technologically changed?

These questions extend beyond the everyday empirical horizons of laboratory work and the utilitarian frameworks of public policy issues. Yet, as technological power gets closer to mastery over the genetic origins of human life, these questions may become increasingly inescapable; philosophical neutrality could become incompatible with the protection of the common good. How public policy will be devised to match this kind of power will stand as an open question for the rest of this century.

Genetics: From Laboratory to Public Forum

The development of recombinant DNA technology in the early 1970s launched a controversy of several dimensions that lasted throughout the decade. The issues at the core of this controversy were debated most openly in the United States. Other countries, such as England and Canada, focused more on issues that could be managed through quiet, administrative efforts. Despite differences among countries in their style of response, the ability to engineer living molecules, to recombine genes from different living species, and to design new hybrid forms of living matter radically changed the public status of molecular biology. Long viewed as a rather esoteric domain of research by lay people, and even by many scientists, molecular biology quite suddenly became the centre of public attention. It was a new experience for the scientists and for the people. That experience has passed several milestones, even if it has not yet run its course.

The scientific community presented this new technology to the general public as a technical triumph. However, both scientists and lay persons also perceived this innovation as threatening. Scientists described recombinant DNA technology as powerful and revolutionary. It would catalyse rapid advances in scientific understanding and major developments in medicine, pharmaceutics and agriculture. Leading scientists expressed divided opinions on the nature, likelihood, novelty, and magnitude of the safety risks this technology presented.

The early warnings of leading scientists are still generally evaluated as admirable expressions of scientific responsibility. Wittingly or not, these warnings were also political acts. They triggered a mobilization, particularly in the U.S., of public consciousness and public involvement in the negotiation of resolutions to an expanding range of issues. Inexorably, the debate spiralled beyond the initial concerns about safety, containment, and regulation to confront the more encompassing question of how the scientific community should relate to the broader human community in a free society. This enduring question, rejuvenated with each new generation and each major scientific innovation, will exert a novel challenge throughout the rest of this century as molecular engineering technology comes closer to mastering the genetic origins of human life.

The protracted, frequently highly vocal, and often virulent controversy on recombinant DNA has quieted. Some issues have been satisfactorily resolved, others are no longer seen as urgent, still others are probably dormant. Questions of another sort, however, are on the rise. European legislators, for example, have proposed that the right to a genetic inheritance free from any form of genetic engineering be adopted by the European Rights Convention. If recognized, should such a right be taken to exclude possible future forms of genetic surgery performed at an early stage of embryonic development to eradicate the genetic basis of an otherwise inevitable genetic disease? Should that right be taken to exclude possible future genetic modifications of the germ line, that is, of the reproductive cells or gametes, to ensure that a person does not transmit a given deleterious gene to descendants?

These and a host of related questions – some novel, others only an intensification of familar difficult issues about the ethics of novel therapies – will ensure the new genetics a central place in the field of public policy for many years. A point of no return has been passed. Those charged with the protection of the common good and with the achievement of the public purpose can no longer afford to remain ignorant of the major concepts; methods, and potentials of molecular biology and genetic engineering.

How did molecular biology and genetics achieve such a high profile in the public forum?

Period of Major Discovery and Public Silence

Discoveries in genetics between the early 1940s and the mid-1960s were critical for the growth of knowledge and technology and were unaccompanied by public discussion or controversy. Three fundamental questions were answered during this period: What is the chemical substance of genes? How are genes structured? What is the genetic code?

Rapid developments in genetics, to which the public has become accustomed in recent years, were set in motion when DNA (deoxyribonucleic acid) began to dominate and direct scientific thinking about the genes. Today, high school students throughout the world know that genes, the carriers of hereditary information from one generation to the next, are made of DNA. Scientists did not know this in the early 1940s.

In 1944, Oswald T. Avery and colleagues demonstrated that DNA had to be the factor of life's chemistry that carried an inheritable character from one strain of pneumococus (a bacterium) to another. This demonstration showed that DNA was the hereditary substance and that genes were made of DNA. This idea did not, however, win immediate acceptance among geneticists. Avery's discovery was premature. A discovery, as Gunther S. Stent has explained, "is premature if its implciations cannot be connected by a series of simple logical steps to canonical, or generally accepted, knowledge."[2] No one quite knew what to do with it, how to proceed with productive experimentation.

The new idea that DNA was the substance of genes was reinforced and established in 1952 when Alfred Hershey and Martha Chase showed that at least 80 per cent of a virus's DNA enters the bacterial cell and at least 80 per cent of a virus's protein remains outside when a bacterial virus infects a bacterium.

At the time of Avery's demonstration, scientists also had difficulty understanding how DNA possessed a chemical structure sufficiently varied and differentiated to carry the wide range of specific information needed to account for hereditary phenomena. DNA had been known for several years to possess units of adenylic, guanylic, thymidylic, and cytidylic acid, units called nucleotides. The central role of these nucleotides in the explanation of DNA's power to transmit highly specific and varied hereditary information began to emerge from obscurity when Erwin Chargaff showed in 1950 that the exact nucleotide composition of DNA differs from one form of life to another.[3]

As a result of the research of these and other scientists, DNA, after 1952, became the central focus for all subsequent work on the nature of the gene. In 1953, James Watson and Francis Crick proposed their now famous model of DNA structure. DNA is made up of two chains of nucleotides intertwined in the form of a double helix. The principle of complementarity explains how the key elements in the nucleotides—the bases adenine (A), thymine (T), cytosine (C), and guanine (G)—are arranged in pairs along the intertwined chains. Adenine pairs with thymine, and cytosine pairs with guanine.

The Watson-Crick model of DNA structure spawned a new generation of research that, by the mid-1960s, solved the fundamental question of the genetic code, that is, how hereditary information carried by the genes, or segments of DNA, is translated to form the roughly 30 000 proteins essential for human growth and function.

The basic idea of the genetic code is quite simple in the light of the following few facts. First, proteins are made from various combinations of 20 amino acids. Second, in human beings and higher organisms, the right combinations of amino acids is put together in a part of the cell called the cytoplasm. The cytoplasm surrounds the cell nucleus. Third, the chemical information needed to combine amino acids comes from the DNA within the cell nucleus. Fourth, this information is coded in the sequence of the nucleotides—A, T, C, and G—of DNA, and is carried to the protein-building part of the cell, the cytoplasm, by messenger RNA (ribonucleic acid). RNA's nucleotides are similar to those of DNA, except that RNA contains uracil (U) instead of thymine.

A code establishes a rule of correspondance between two or more sets of symbols. The genetic code sets up a correspondence between two chemical alphabets: the four-letter alphabet of messenger RNA, consisting of adenine, uracil, cytosine, and guanine, and the 20-letter alphabet consisting of the 20 amino acids. Groups of three nucleotides, for example, AUG, GGC, called "triplet codons," deliver the information to determine which amino acids will be synthesized in what order to form which proteins.

These critical discoveries and advances in genetics took place within a period unmarked by public debate or controversy. One might say that these discoveries were socially premature in an analogy with the scientifically premature character of Avery's discovery in 1944, as explained by Stent. The implications of these discoveries, to paraphrase Stent, could not yet be connected, via a series of imaginable or reasonable extrapolations, to the common good or the public purpose. The power of genetics had not yet dawned.

Genetic Engineering: The Emergence of Speculation and Concern

During the debates on recombinant DNA in the 1970s, Maxine Singer, after mentioning the failure of scientists to educate the public adequately, observed: "It should not then be surprising if deep fears and ambiguities arise in the minds and hearts of those who suddenly learn the depths of modern insights into the nature of living things."[4]

From the mid-1960s, scientists and practitioners of disciplines such as law, ethics, philosophy, and theology took the initiative to draw the attention of the educated general pbulic to momentous happenings in molecular biology. As people began to learn about the depths of modern insights into the nature of living things, seminars, symposia, and a wide range of individual essays took up the themes of genetic engineering, genetic manipulation, genetic therapy and genetic control. Several examples from this extensive and continuing literature document the dawning of speculation and concern.

Robert Sinsheimer's 1966 article, "The End of the Beginning," raises the theme of rational, that is, genetic, control of human structure and function.*

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* In the article, the paragraphs preceding this quotation deal with genetic therapy and the control of growth and aging.

> And in the end, after all those smaller steps to improve man's lot are taken, we may come to change man himself, his physique, his emotions, his intelligence, all of which are, in large part, the outcome of an inheritance pattern. Which too can come under rational control. Not tomorrow. Perhaps not this century or the next. But it is only three centuries since Francis Bacon, and there are many centuries ahead.[5]

Salvador Luria, a Nobel Prize-winning microbiologist and Sedgwick Professor of Biology at the Massachusetts Institute of Technology, stated that molecular biologists have made "the genetic mechanism directly available to chemical experimentation . . . Obviously such knowledge, which reaches to the most intimate level of the hereditary mechanism, can generate a new and powerful genetic technology."[6]

In an article in the *National*, Luria emphasized the awesome possibilities of "true genetic surgery — the artificial correction, replacement, removal or addition of genes, based on discoveries of molecular biology."[7] He then identified the truly controversial social applications that might be envisioned:

> If it becomes possible to manipulate the genes of the human germ line or to achieve artificial fertilization and nuclear transplantation with human eggs, we would be faced with the terrifying responsibility of deciding what we — the human race — intend to become. At the start, we may simply remove defective genes or replace them with their normal counterparts. Then we may start to fool around by introducing supposedly "desirable" genes.[8]

In 1968, the *UCLA Law Review* published Martin P. Golding's "Ethical Issues in Biological Engineering." One of Golding's main warnings immediately follows his plea for mutual confidence between layman and biological scientists.

> It is in the field of biological engineering that we are likely to have a crisis of confidence. Control over the direction of mutation, which is possible now in limited areas, is bound to be extended. If it has not already been done, babies will be grown in test tubes. The imagination is staggered by the possibilities — for evil as well as good. Both positive and negative eugenics, which are the products of benevolent if often misguided

> men (in my opinion), will be overtaken by atypogenics, the creation of the abnormal, the weird, and the bizarre. It is generally true that any new technique which is discovered is put to use. The strange world of the science fiction writer will become a reality.[9]

These few quotations are only a small sample of the extensive literature of awakening that arose during the 1960s and early 1970s. These writings have a literary genre of their own. They occupy a place in a long tradition of prophetic interpretation. Whatever the merits of any individual essay, these writings, as a body of literature, represent exercises of intelligence attempting to foresee where science is heading and the dangers society may have to encounter. The language of these essays, often inflated and promethean, was designed to stir and grasp the attention of a sleeping people. Luria's emphasis reveals this purpose. He called for a leadership that would "find the way to awaken the public and their elected representatives from the complacency that lies behind the distorted priorities of present-day society."[10]

This kind of writing achieves its cultural purpose when it awakens and mobilizes the people to participate effectively in defining the public values, purposes, and corresponding new institutions needed to master the novel powers of scientific and technological innovation. The arrival of recombinant DNA offered the first major test from the domain of molecular biology of how society would respond to a new technology characterized by risks and benefits that were, at the outset, largely conjectural.

Recombinant DNA in the Public Forum

The Gordon Research Conference on Nucleic Acids, held in June 1973, announced a technical innovation in molecular genetics: the ability to fabricate biologically active or living hybrid molecules by recombining genes from different forms of life. The techniques came to be known as recombinant DNA technology, or simply, recombinant DNA.

Scientists speak of genes as DNA molecules made up, among other things, of the nucleotides adenine, thymine, cytosine, and guanine. Lay people think of genes as the building blocks of life, especially human life. Changes in these building blocks mean very remarkable differences in the appearance, health, and capabilities of human beings. Gene changes or mutations of the nucleotide sequences have taken place throughout the history of life on this planet. These changes always took place randomly, however, human beings learned long ago to breed plants and animals to take advantage of favourable random genetic mutations, but a technology had never been developed that permitted human beings to direct the process of mutation itself.

This is the significance and the power of recombinant DNA technology: the ability to manipulate the chemistry of life, to modify the nucleotide sequences defining the hereditary messages that genes transmit from one generation to another. Although this technology is still young and the kinds of life to which it is currently applied are lowly and limited in number, one should recognize that this technology, in combination with other skills and techniques, means the dawning power to modify inheritance.

Initially, recombinant DNA technology entered the public forum, primarily in the U.S., as an issue of safety, control and regulation, rather than as an issue of responsibility for power over inheritance. Letters from eminent scientists, published in leading science journals, expressed deep concern over potential biohazards arising from recombinant DNA experimentation. The untested, hence uncertain, properties of biologically active, new genetic combinations prompted the concern about the safety of laboratory workers and the general public.[11] One letter recommended a moratorium on certain particularly dangerous kinds of recombinant DNA experiments, called for an international meeting of scientists to discuss ways of dealing with recombinant DNA hazards, and requested the U.S. National Institute of Health (NIH) to devise guidelines for investigators working with recombinant DNA techniques.[12]

Held in February 1975, at the Asilomar Conference Center, Pacific Grove, California, this international meeting of molecular biologists, with lawyers and journalists present, was called the International Conference on Recombinant DNA Molecules. The meeting came to be known as the Asilomar Conference. The conference report, published on June 6, 1975, contained a paragraph remarkable for its prescience on the course that would be followed to ensure protection from biohazard. The report stated that:

> . . . the participants at the Conference agreed that most of the work on construction of recombinant DNA molecules should proceed, provided that appropriate safe-guards, principally biological and physical barriers adequate to contain the newly created organisms, are employed. Moreover, the standards of protection should be greater at the beginning and

> modified as improvements in the methodology occur and assessments of the risks change. Furthermore, it was agreed that there are certain experiments in which the potential risks are of such a serious nature that they ought not to be done with presently available containment facilities. In the longer term serious problems may arise in the large-scale application of this methodology in industry, medicine, and agriculture. But it was also recognized that future research and experience may show that many of the potential biohazards are less serious and/or less probable than we now suspect.[13]

After the Asilomar Conference recommendations, guidelines and regulations of various sorts were devised in North America and Europe and implemented in ways peculiar to each country involved. In Britain, the report of the Ashby Working Party in 1975 was followed by the establishment in 1976 of the Genetic Manipulation Advisory Group, a central advisory body in charge of deciding about recombinant DNA experiments case by case. In the U.S., the National Institute of Health with its Recombinant DNA Advisory Committee, published guidelines in 1976. Though quite stringent initially, these guidelines were subsequently relaxed, as was foreseen in the Asilomar report. In France, the Commission de Contrôle de la Délégation Générale de la Recherche Scientifique et Technique published a simple set of guidelines in 1977. The Medical Research Council took the lead in Canada and published its first, and subsequently modified, set of guidelines early in 1977. In Europe, transnational groups, such as the European Molecular Biology Organization, the European Science Foundation, and the Commission of the European Economic Community, studied the issue of safety and regulation and issued appropriate recommendations.

The point of this list is to emphasize that many people in various parts of the world directed their organized attention to the conditions required for responsible recombinant DNA research. Opinions in many matters and styles of regulation differed, sometimes sharply. In a study of England, the U.S., and Canada, Howard Eddy observed:

> External factors of political tradition and power almost completely dictated the U.S. and British response to the controversy. In Canada, the "non-controversy" status of recombinant DNA allowed handling the

> issues through normal bureaucratic channels. They were well handled. But the limits of the challenge defined the scope of the possible response. Thus, of all the countries studied, Canada has had the least rehearsal of the issues being raised by biotechnology."[14]

The emphasis on various recombinant DNA issues shifted during the late 1970s and early 1980s. The cluster of controverted questions about safety and regulation led to public discussions, particularly in the U.S., about patenting rights on new forms of life fabricated in the laboratory, about the propriety of emerging industrial-academic-corporate connections motivated by biotechnology's growing commercial power, and about the ethics of an attempt, generally judged to have been premature, at human genetic therapy.

The political question at the crux of the controversy on recombinant DNA, expressed most strongly in the U.S., was how the scientific community should relate to the broader political community and how citizens without scientific expertise can most effectively participate in decisions about powerful new technologies. These issues were not new, but they acquired new urgency because of the life-controlling power of this new technology and because of the dramatic and thought-provoking commentary of eminent scientists and scholars.

Molecular biologists glimpsed a new future for their science. They saw recombinant DNA opening new horizons for highly productive experimentation in many directions. The new gene technology would open pathways to a radically new medicine. Short of genetic therapy, applications of recombinant DNA held the promise of tangible medical benefits and considerable commercial profit for companies, individual scientists, and universities. The linking of recombinant DNA to genetic engineering triggered extrapolative leaps and incited the flames of long-range concerns. Respected scientists, not only those with expertise in molecular biology, emphasized the need for critical reflection on the new power released by recombinant DNA technology.

The momentous and ethically difficult questions of responsibility for the biosphere and the future of human nature disappeared at times during the controversy over recombinant DNA. These questions are surfacing again as concern about responsiblity for power over the genetic correlates of distinctively human characteristics. By demonstrating that the chemical and genetic material of human life is, in an elementary form, interchangeable with all other life, molecular biology has raised the issue of reductionism once again and with renewed force. Who should decide what levels of human development should serve as norms for the manipulations of the chemistry of human life?

Gene Technology: State of the Art

Genes and DNA: The Basics

Genes perform basic functions that influence all the activities of life. Genes direct their own reproduction as cells divide and multiply. They govern the differentiation of cells to form the various tissues and organs, and they dictate the synthesis of the body's proteins. The proteins are essential, because, as Paul Berg explained, "an organism's phenotype, i.e., its metabolic capabilities, physical endowments and appearance, and even the susceptibility to infection, heart disease, and cancer, are consequences of the battery of structural, catalytic, and regulatory proteins that result from the expression of its genes."[15] Genes determine the programs for the many forms of life.

Genes are made of DNA, life's master substance. The nucleotides are the building blocks of the DNA molecule and of the genes, which are segments of one of DNA's two intertwining chains of nucleotides. Genes differ according to differences in the order of sequence of these nucleotides – A, T, C, G – in various segments of DNA. A structural gene may consist of several thousands of these nucleotides.

The genetic message carrying hereditary information from one generation to the next is coded in particular DNA sequences of A, T, C, and G. The genetic code sets up a series of construction commands issued in sets of three nucleotides. For example, the sequence of the three nucleotides TAC in DNA determines the structure of the messenger RNA codon as AUG, which is a command to the cell's protein factory to use the amino acid methionine at the next step in the assemblage of a protein. The sequence of the codons dictates the sequence of the amino acids. Both determine the structure of the protein.

Some sequences of nucleotides in DNA determine which amino acids are to be combined in which order to synthesize the various proteins. Other sequences of nucleotides define the regulatory commands, "start here" and "stop there," governing both the process of transcription of DNA into messenger RNA and the process of translation of messenger RNA into protein synthesis. There are still other kinds of commands to control when, and in which type of cell, specific genes should be used.

It was thought, until recently, that the sequences of nucleotides that make up a structural gene-that is, the sequence of nucleotides carrying the information for the formation of a protein out of amino acids-was an unbroken and contiguous segment of DNA. This is true for bacteria, but the genes of higher forms of life are much more complex. The structural genes in these forms of life are split into segments that are separated by intervening stretches of DNA.[16] The segments that make up the structural gene are called exons and the intervening sequences are called introns.

DNA is the master substance in the cells of all organisms. The number and sequence of the nucleotides of DNA specify the remarkably different genetic blueprints that result in bacteria for bear, mice or men.

Recombinant DNA and Molecular Cloning

Recombinant DNA is essentially a set of methods for the construction of biologically functional DNA molecules combining genetic information from different sources. The new molecule is called a recombinant DNA molecule because it results from the combination of two different segments of DNA nucleotide sequences.

Along with its closely related technique of gene or molecular cloning, recombinant DNA can be a tool for gene study and an instrument for genetic engineering. The technology for recombining segments of DNA molecules from different sources actually is a tool kit of its own, consisting of several quite different biochemical and biological operations. As explained by Stanley Cohen in a *Scientific American* article, recombinant DNA technology is a procedure with four related steps requiring:

- a method for separating and joining DNA molecules coming from different sources
- an appropriate carrier that can integrate the DNA that is to be spliced-in or recombined and replicate both itself and the foreign DNA fragment that has been linked to it
- a method of introducing the recombined DNA molecule (the gene carrier plus the spliced-in DNA fragment) into a functional bacterial cell
- a selective mechanism that permits recovery from a large population of cells precisely of those cells that contain the recombined DNA molecule[17]

These four requirements and the procedures for which they are needed constitute a two-phase technology: DNA recombination and molecular cloning. These phases are closely related. Planned or directed molecular cloning would be impossible without the preliminary technique of DNA recombination; and it would be difficult to do anything significant, either for theoretical or practical purposes, with recombinant DNA molecules if one did not have molecular cloning or copying for their amplification. This two-phase technology has been called genetic manipulation or genetic engineering. Genetic engineering now encompasses both this basic technology as well as its many new applications.

Gene Transfer

The concept and a particular form of gene transfer have already been introduced. The section on DNA recombination and molecular cloning mentioned that a gene or segment of DNA could be linked to a carrier, such as a plasmid (a non-chromosomal form of DNA), and transferred to a bacterial cell. Gene transfer was known and practised even before the advent of recombinant DNA technology. Much progress distinguishes today's technology, however, from earlier bulky and untargeted transfers of DNA.

Three lines of advance and a new horizon of applications are particularly notable. First, because of recombinant DNA technology, specific genes, rather than clusters of unknown genes, can now be transferred to target cells. Second, appropriately specific transfer procedures are also available and in use. Three methods of so-called DNA-mediated gene transfer now permit the targeted transfer of specific genes into cells, not only into lines of cells cultured in the laboratory, but also into the body cells and germ-line cells of living animals. Third, an expanded range of target cells widens the horizons of research and potential applications.

Each successful transfer of a gene from one species to another has been hailed as revolutionary or, at least, as highly innovative and ingenious at the time of its public announcement. The transfer of the human genes for insulin and for growth hormone to bacterial cells, for example, was such an event. A second field of expansion opened up when living mammalian cells cultured in the laboratory were successfully transformed by gene transfer methods. For example, a TK (thymidine kinase) gene from herpes simplex and a human beta-globin gene were successfully transferred to a TK deficient mouse cell. This kind of gene transfer is now common.

Functioning genes have also been successfully transferred into the living mammalian fertilized egg. Scientists recently micro-injected the rabbit gene for the protein beta-blobin into the male pronucleus of mouse eggs shortly after fertilization. The rabbit gene worked in the resulting grown mice and was transmitted to the offspring produced by these mice. "The latest work represents another significant advance in that introduction of a new gene into a recipient of a different species and germ line transmission were achieved in the same experiment."[18] The recent successful introduction of rat and human growth hormone genes into fertilized mouse eggs offers even more striking examples of a growing scientific ability to modify mammalian embryos genetically. Mice carrying the gene for human growth hormone grew more rapidly than other mice to attain a size twice that of normal.[19]

It would be difficult to overestimate the power and promise of gene transfer technology. Recent advances are opening pathways for projects that would have been impossible several years ago. This transfer technology is amplifying scientists' ability to map the genes of mammalian cells, the human cell included. It is the most promising tool presently available to determine how gene expression is regulated. Moreover, the successful transfer of functioning genes into living animals brings genetic therapy and agriculturally profitable forms of genetic engineering closer to realization.

Gene Mapping

One needs maps to find objects situated among many others of a kind in complex spatial arrangements, such as streets in a large city and cities in a province. An analytical table of contents in a large book helps the reader find a passage of interest among the hundreds of other paragraphs bearing no relation to the purpose at hand. One also needs maps of a special kind to find genes within the cell.

To map a gene means to locate its position on a chromosome. The normal human cell, as scientists have known since the mid 1950s, has 46 chromosomes. These are arranged in 22 pairs of non-sex chromosomes, the so-called autosomes, and one pair of sex chromosomes, XX in females and XY in males. In human beings and in other higher organisms, the chromosomes are located within the nucleus of the cell.

A chromosome is basically a length of intertwined strands of DNA. A chromosome is an ordered assemblage of genes, somewhat as a chapter is an ordered assemblage of words. In turn, a gene is an ordered composition of the nucleotides, A, T, C, G, somewhat as a word is an ordered composition of letters. The X chromosome, for example, contains roughly 100 000 000 nucleotides. The number of genes, obviously, is considerably less.

The path of the search served by gene mapping and sequencing is illustrated in Figure 1. Although approximately 3400 human genes have been identified, not all have yet been mapped to specific chromosomes and specific regions of chromosomes. The report in November 1983 that the gene involved in Huntington's disease is located on chromosome 4 in humans is an example of a recent addition to the human chromosome map.[20] Until the late 1970s, human gene mapping was a relatively slow process, with about four genes being mapped per month. The development of new mapping methods will certainly speed up the process in the next few years.[21]

The long-term objective is a complete map of human genes, as Bob Williamson explained in *Nature*:

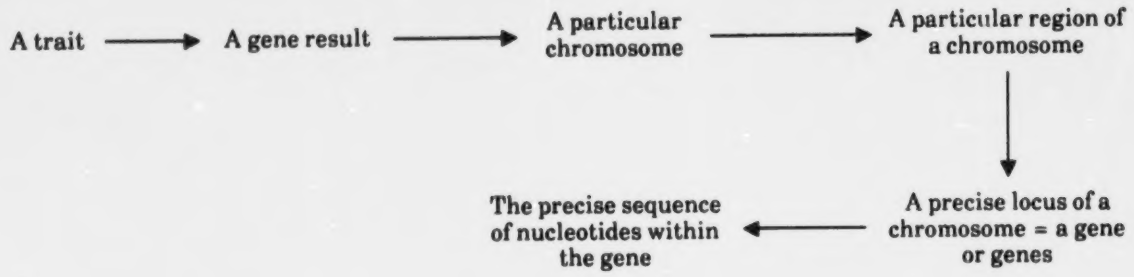
> When a total gene map exists, McKusick predicted that it will be possible to carry out "reverse diagnosis", from gene to phenotype. This will be particularly useful in the diagnosis of dominant diseases, such as Huntington's chorea, where persons at risk live with anxiety for many years before finding out whether the disease develops in middle age.[22]

One can imagine the diagnostic applications of a total gene map as well as the attendant ethical dilemmas that will arise. It is easy to surmise that such a store of highly detailed information will affect the future course of medicine, even if it is difficult to delineate clearly what the specific effects will be. Writing in *Science*, Paul Berg forecast that a new and quite different kind of medicine will appear on the horizon in the near future:

> Already, investigators have isolated a number of mammalian and human genes, and in some instances determined their chromosomal arrangement and even their detailed nucleotide sequence. Such detailed information has profound implications for the future of medicine. Just as our present knowledge and practice of medicine relies on a sophisticated knowledge of human anatomy, physiology, and biochemistry, so will dealing with disease in the future demand a detailed understanding of the molecular anatomy, physiology, and biochemistry of the human genome.[23]

How far are scientists from a total human gene map? Not very far, according to one expert who predicted that "the human gene map should be completely defined" by the early 1990s.[24]

FIGURE 1
Gene Mapping


A trait
A gene result
A particular chromosome
A particular region of a chromosome
A precise locus of a chromosome = a gene or genes
The precise sequence of nucleotides within the gene

Gene Sequencing

One could neither read nor write if ignorant of how the letters of the alphabet are arranged to form words. Gene sequencing reveals how the nucleotides are arranged to form a gene. It is the key to "genetic literacy," to the ability to read and write genes.

Rapid DNA sequencing, or speedreading of genes, is possible because of two methods, one from the work of Allan M. Maxam and Walter Gilbert of Harvard University, the other developed by Frederick Sanger and colleagues at Cambridge University.[25] Scientists can now sequence DNA lengths of up to 200-300 nucleotides in one experiment. Both methods use X-ray film images of DNA fragments to reconstruct the original sequence of nucleotides of the genes under study. What could only have been dreamed about in the early 1970s can now be achieved. These new methods enable scientists to determine the molecular structure of eucaryotic genes, the genes of human or other higher forms of life.[26]

The human mitochondrion, a small rod-shaped structure in the human cell, offers an example. The complete sequence of the genes in this structure, the human mitochondrial genome, has been determined. It is 16 569 base pairs long. When one considers that the genome, the total collection of genes, in the bacterium Escherichia Coli is about 10 000 kilobases, or 10 000 000 bases, in length, it is easy to grasp that DNA sequencing is only at the beginning of a long road. One destination far down that road is the DNA sequencing of the complete human genome, a task that would have to cover approximately 500 000 kilobases, or 500 000 000 bases.

The sequencing of DNA is only part of the more complex goal of understanding correlations between the DNA sequence, the three-dimensional structure, and the function of genes. Computers are already useful in DNA sequencing work and will become indispensable as larger and more complex sequencing programs are undertaken. A common problem, however, of automated systems – the separation of the human agent from primary data – may be compounded as computers are used at various stages of gene analysis. An automated gel reading system, now ready for the market, may still merit an earlier warning for caution "because it effectively separates the investigator from the examination of his primary data."[27]

A Total Human Protein Map?

Brian Clark, writing in *Nature*, explained that a total human protein map or catalogue "could make it possible to detect metabolic irregularities and diseases, such as cancer, which affect gene expression."[28] To make such a catalogue, one has to separate, identify, measure, and name the proteins and enzymes resulting from gene expression. This involves an enormous amount of data that has to be stored in some usable form. Scientists have thus far separated and catalogued about 1200 of the estimated 30 000 human proteins. One may readily understand why a total human protein map has been called a large-scale challenge.

DNA Libraries

Some of the world's oldest and best libraries possess only fragments, not complete texts, of the works of ancient writers. Diels's edition of the fragments of the pre-Socratic philosophers is an example. Barring some remarkable archeological find, these fragments are all the world will ever know of these works because the complete originals have been lost or destroyed.

Genetic "libraries" also conatin only fragments of genetic messages (copies at that), but their potential for acquisition is great. The complete genetic texts of human beings and other life forms exist and are reproduced ever anew, with slight but individually significant modifications. Barring a total nuclear catastrophe or an equally lethal disaster of some other kind, these texts should always be available.

The DNA libraries are growing quite randomly, somewhat as a personal library grows as interesting volumes come to one's attention for purchase or come into one's possession as gifts.

Recent technical advances linked to recombinant DNA procedures give access to interesting and highly important fragments from complex genetic messages characteristic of higher living forms (in eucaryotic cells). Collections of these "cloned" fragments or fragment copies are now being assembled. A library of 50 000 recombinant fragments has already been constructed from X chromosomes. Newer florescent dying techniques and special instruments will permit the building of similar libraries of the other human chromosomes, the autosomes. The task is not altogether unlike that faced by scholars trying to decipher the letters of an ancient text obscured by the accumulated, crusted debris of centuries.

These DNA libraries are of the utmost value. Without them scientists will remain genetic illiterates, unable to read the messages of the genes and unlikely ever to rewrite them. There is an urgent scientific need for these libraries, or banks, as they are sometimes called. The rapidly accumulating fragments of DNA text produced by gene sequencing techniques underscore this need. An editorial in *Nature* made this appeal: "What does not yet exist is any central data bank in which all sequences could be deposited and made freely available to the whole scientific community. . . . It matters little by whom, or where, a bank is started. What is important is that it should start soon."[29] The European Molecular Biology Laboratory made a start, announcing the formation of a nucleotide sequence library.[30]

In August 1983, NIH awarded a $3-million contract over five years to the company Bolt, Berenek and Newman in Cambridge, Massachusetts, to establish the national data bank, now called GenBank. NIH also awarded $5.6 million to the company IntelliGenetics to set up a national computer resource for molecular biology. BIONET, as this new system is called, will offer many services designed "to establish a community of molecular biologists who can communicate rapidly, effectively, and frequently with each other over a computer network."[31]

Not only scientists but also educated laypersons outside the medical sciences should be able to recognize the need for these libraries. They "will be particularly useful for the investigaton of genetic diseases such as Duchenne's muscular dystrophy, where the basic defect has not been elucidated, and a neoplasia, where several specific chromosomal anomalies, particularly for the leukemias, have been identified."[32] Eventally, these libraries will be the basis for a revolutionary new form of medicine. If scientists are still illiterate genetically, they are also still quite primitive medically; but it is unlikely they will remain so.

Gene Synthesis

The ability to synthesize genes in the laboratory is equivalent to the ability to write genetic messages. As scientists are perfecting their skills in reading the genetic messages already written by nature, they are simultaneously learning how to rewrite nature's genetic compositions, not only how to copy those that nature has dictated.

A first method of gene synthesis is enzymatic copying, a process that utilizes enzymes and works backward from messenger RNA to produce a DNA sequence of nucleotides. A second method, total gene synthesis, uses chemical synthesis to produce blocks of nucleotides that are then joined to produce a total gene. These methods can also be combined to profit from the advantages of each. It was a combination of these methods that was used along with recombinant DNA techniques to produce human growth hormone from bacteria.[33]

Although one can foresee with relative ease the immediate potential of gene synthesis for basic and applied research, it is quite difficult to imagine the long-term effect of these powerful new skills. The method of total gene synthesis, for example, offers the striking power "to introduce specific alterations into the gene structure and to study the effect of such 'mutations.' "[34] Directed mutagenesis means the ability to change genes in a directed, nonrandom, precise way.

Some scientists, with due homage to what has been achieved to date, believe the best is still to come. Others are less sanguine about the ability of human beings to manage great power wisely; they may wonder if it is the worst that is to come.

Part of that "best to come" may emerge from the power gene synthesis gives to direct gene change. "Chemical DNA synthesis allows essentially complete flexibility with regard to gene manipulation and construction."[35] Total gene synthesis permits "the creation of new information," that is, new genetic information.[36]

The immediate effect of gene synthesis is on basic research. It provides "systematic approaches to the precise studies of the control regions in different systems."[37] The approach of gene synthesis, however, "may be the only one that enables a deeper understanding of biological controls at the molecular level."[38]

Gene synthesis contains a power for applied research that is difficult to measure or precisely delimit. The application of automated methods to gene synthesis will undoubtedly hasten the realization of these applications. As noted above, genes produced by total chemical synthesis or by a combination of chemical and enzymatic synthesis can function in bacterial cells to direct the production of protein. This has been achieved for several important proteins, such as human somatostatin (a modulator of growth hormone secretion), insulin, and growth hormone.[39] One researcher has observed that "in addition to the possibility of producing proteins of known importance, . . . chemical synthesis of genes offers the capability of experimentally creating new polypeptides and enzymes with potential medical and industrial applications. Realization of this potential depends on the ability to produce DNA sequences rapidly and economically."[40]

Potential applications of more mature technology for gene synthesis may well raise difficult philosophical and ethical questions. Prophetic warnings and cries of "Armageddon" express exaggerated fears, though scientists may be well advised to establish direction and goals for their use of genetic information.

Genetic Engineering

The Fact

The preceding discussion has described the technologies and procedures that make genetic engineering possible. The projects that are achieved by the use of recombinant DNA – molecular cloning, gene transfer, gene mapping, gene sequencing, and gene synthesis, along with ancillary techniques – are what is meant by genetic engineering. Genetic engineering, once only a possibility, has been a fact for several years. The *Harvard Medical School Health Letter*, a publication directed to the general reader, made the following announcement in 1981.

> Every time science fiction writers gather, they remove one or two items from their list of futuristic dreams – mostly because modern science has converted yet another fanciful idea into reality. A few years ago, genetic engineering was still science fiction. Today, it has become not just one, but *two* realities: a powerful new tool for medical research and a controversial new social issue.[41]

The above claim is too modest because it is incomplete. Genetic engineering, as seen in the preceding section, has been and is still primarily a tool of basic research in molecular biology. The goal, for example, of most researchers using gene transfer, one of the key instruments of genetic engineering, "is to study the control of gene expression in mammalian cells, one of the more recalcitrant mysteries of molecular biology."[42]

By 1980 genetic engineering had become an indispensable tool of agricultural research. Of 40 research grants, listed in *Food and Agriculture Research Grants in the U.S. for 1980*, 20 were for projects employing one or several aspects of genetic engineering. Several project titles relaying this message are: "Isolation and Characterization of Coding Regions from Plant Genomes"; "Development of Gene Transplant Technology for Crop Plants"; "Gene Transfer from Wild Grasses to Barley, *Hordeum Vulgar L.*"[43]

That genetic engineering is now a highly prized tool of pharmaceutical and industrial research should be obvious to anyone who reads newspapers and news magazines. A host of articles have transmitted a message similar to the following from *Newsweek*'s 1980 article "The Miracles of Spliced Genes":

> The technology, popularly known as recombinant DNA, is only about seven years old, but it has already

> become almost routine. In laboratories all over the world, biologists are taking genes from one organism and planting them into another. So far, the gene splicers have succeeded in inducing bacteria to make human insulin and several other hormones. And that's only the beginning. Someday, bacteria will be turned into living factories: they will churn out vast quantities of vital medical substances, including serums and vaccines, to fight diseases ranging from hepatitis to cancer and the common cold.[44]

The production of hormones and vaccines, for all their importance, neither exhausts nor defines what is meant by claims that genetic engineering is a powerful tool of medical resarch. Medicine has two major phases: diagnosis and treatment, which, at its best, achieves a cure. Genetic engineering is already expanding the range of genetic anomalies that can be diagnosed both before and after birth. The goal is a total mapping of the molecular etiology or correlates of disease. The ultimate goal inscribed in the logic of genetic engineering as a medical research tool would be the cure of molecular disease. Factor VIII, for example, a protein that is part of the normal blood clotting process, is missing in persons suffering from hemophilia. The direct implantation of the missing functional genes into persons with hemophilia, so that they could produce their own factor VIII as normal people do, is an ultimate goal of genetic engineering.

An intermediate goal, the commercial production of virus-free, genetically engineered factor VIII, is now closer to realization. In a collaborative effort, scientists from three institutions, Genentech (San Francisco), the Hemophilia Centre at the Royal Free Hospital Medical School (London), and Speywood Laboratories (Wales), have succeeded in cloning the gene for factor VIII, introducing the clone into a mammalian cell line, and achieving the production of this much needed blood protein. Of course, it will take several years before enough factor VIII is produced to launch clinical trials and then to supply the needs of those affected with hemophilia.[45]

The Fields

Genetic engineering—the designed modification of the gene complement of living forms—has to date been successfully attempted numerous times in bacterial cells, mammalian cells, and mammalian embryos. It has also been performed twice in the human body with no report of successful results.

Genetic engineering in bacterial cells. The early experiments with recombinant DNA, schematically described in earlier sections of this chapter, were examples of genetic engineering in bacterial cells. One of these early projects succeeded in splicing genes from the toad *xenopus laevis* into a plasmid (small circular molecules of DNA, found in bacteria and yeast) and reinserting this plasmid into its bacterium. The genes selected were those that code for or produce a precursor of the ribosome. (The ribosomes are structures in the cell upon which the proteins are synthesized.) As the plasmids were replicated within the bacteria, so also were the toad genes. What is more, these toad genes were being transcribed into a toad RNA product within the bacterium. The bacterium had been genetically engineered to produce toad RNA.[46]

Since these early experiments, similar recombinant DNA and molecular cloning methods, augmented by gene synthesis techniques, have successfully engineered bacteria with the human genes for somatostatin, insulin, growth hormone, and interferon, a protein with many potential therapeutic applications.[47] The bacteria produce the human hormone. These results combined with the phenomenal reproductive rate of bacteria offer industry revolutionary new methods of producing hormones previously fabricated only by the human body. Human growth hormone produced by these methods has already reached the phase of clinical testing.[48] As mentioned above, the use of similar methods may soon result in the commercial production of factor VIII, the blood protein needed by those suffering from hemophilia.

Genetic engineering in cultured mammalian cells. The techniques used for inserting genes into the cells of higher living forms, into the cells of mammals, or into so-called eucaryotic cells have already been described in the section of this chapter on gene transfer. These techniques permit more highly advanced genetic engineering.

As discussed, Paul Berg and colleagues used the recombinant virus technique to insert rabbit genes for rabbit beta-globin into a cultured line of African green monkey cells.[49] Michael Wigler and colleagues used the DNA precipitate method to insert the herpes simplex virus gene for the enzyme thymidine kinase into a line of mouse L cells lacking this gene.[50] W. French Anderson and Elaine G. Diacumakos used micro-injection to insert a gene for thymidine kinase and a gene for human beta-globin into a mouse L cell.[51] Carol Lynn Miller and Frank H.

Ruddle modified mouse cells with genes from the human cell line named He La S3 using chromosome-mediated gene transfer.[52]

These achievements of genetic engineering in mammalian cells constitute several steps in the direction of genetic therapy for human genetic diseases. The moment for expansive hopes or fears has not yet arrived, however. As Anderson and Diacumakos observed, "Genetic engineering in mammalian cells still has a long way to go."[53]

Genetic engineering in mammalian embryos. Genetic engineering in mammalian cells may have a long way to go but it is advancing rapidly. A still higher form of genetic engineering has been achieved with mouse embryos.

In August 1981, Erwin F. Wagner, Timothy H. Stewart, and Beatrice Mintz reported that they had successfully micro-injected an adult human beta-globin gene and a herpes simplex virus gene for thymidine kinase into the pronucleus of a fertilized mouse egg. (The pronucleus is an intermediate body formed during the process of fertilization before the end-product, the single fertilized cell containing the chromosomes from both parents.) After autopsies were performed on 33 mice in the late fetal stage, the report concluded: "Thus, pure recombinant genes introduced into mice at the onset of their development can remain intact and be stably incorporated and even expressed."[54]

Two months later, Thomas E. Wagner, Peter C. Hoppe and colleagues reported on their successful transfer of a rabbit beta-globin gene by direct micro-injection into the male pronucleus of mouse zygotes, or into a fertilized mouse egg.[55] These fertilized and genetically engineered mouse eggs were brought to term and, after they reached adulthood, were mated. The offspring of these mice were also found to carry and express the rabbit beta-globin genes that had been injected into one of their parents. This experiment represents a successful genetic engineering of the germ cell line, not only the body cells, and, thus, the genetic engineering of future generations.

One commentator on this work emphasized that it "represents another significant advance in that introduction of a new gene into a recipient of a different species and germ line transmission were achieved in the same experiment. Both of these milestones had been accomplished separately ... but, at least as far as published reports go, not together."[56]

In November 1981, Franklin Constantini and Elizabeth Lacy reported that they had inserted adult rabbit beta-globin into the germ line of mice. "We have analysed 24 mice derived from eggs microinjected with this DNA. Nine mice contain the rabbit beta-globin gene in liver DNA, and at least four males from this group transmit the gene to a fraction of their progeny."[57] As noted above, the gene for human growth hormone has been successfully inserted into a mouse embryo.

These successful genetic engineerings of somatic and germ-line cells of mammalian embryos, early in their development, promise greater advances in the understanding of how genes are regulated and how genes control development. Once again, however, "The wider implicaitons are enormous. Leaving aside the controversial question of gene therapy in humans, it seems certain that the genetic manipulation of agriculturally important animals will quickly follow, since, in cattle at least, the techniques of super-ovulation and reimplantation in foster mothers are now routine procedures."[58]

One should not dismiss the possible application of these techniques to the human embryo early in its development. As will be analysed in the section on public policy issues, there is wide moral support for research on the early human embryo (up to two weeks after fertilization) that utilizes the techniques of in vitro fertilization.[59]

Genetic engineering in the adult human body. In July 1980, Martin J. Cline, M.D., and Winston Salser, Ph.D., chief members of a research group at the University of California, at Los Angeles, attempted to modify genetically the bone marrow of two women suffering from beta-O thalassemia. This experimental operation was the first serious effort to engineer the adult human body genetically, using the procedures developed since 1972.

The two patients, a 21-year-old woman in Jerusalem and a 16-year-old girl in Naples, were afflicted with a particular form of the hereditary blood disease thalassemia. This disease particularly afflicts people living in the Mediterranean region, derviving its name from *thalassa*, the greek word for sea, and *anemia*. Persons with beta-O thalassemia produce little or no beta-globin. They are kept alive with regular blood transfusions. Such patients have a limited life expectancy, death frequently occurring in the early twenties. The reports claim that the two patients in this experimental attempt at gene therapy had a one- to two-year life expectancy. Anemia, disfiguring bone deformities, and painful fractures are major disabilities accompanying this disease. Death is most often caused by the build-up of iron deposits in heart tissue. Procedures to remove these deposits, called chelation therapy, though improved in recent years, merely postone early death.

The object of the experimental operation was to implant the human genes for beta-globin into the bone marrow of the two patients. The bone marrow of these patients lacked these genes, and hemoglobin is normally produced in bone marrow. From several reports in science journals and in the absence of a detailed report from the researchers themselves, one can draw the following outline of the steps followed in this experimental attempt at gene therapy.[60]

- Bone marrow cells were extracted from both patients and transformed with the genes from human beta-globin. This means that these genes were inserted into these cells.
- Another gene, the gene for the enzyme thymidine kinase from the herpes simplex virus, was also inserted into these bone marrow cells. The object of this step was to give these cells a better chance to proliferate in the presence of the other non-transformed bone marrow cells in the patients' bodies.
- These transformed cells were then reintroduced into the patients' bodies.
- The patients were subjected to thigh-bone radiation, in doses considered to be unharmful, to create space for the gentically transformed cells to proliferate.
- To all appearances, the human gene for beta-globin and the viral gene for thymidine kinase were introduced in recombinant form, not as naked genes, into these bone cells. The recombinant form uses a plasmid as a vector, or carrier.

This gene therapy experiment drew a barrage of criticism from the medical and scientific community.[61] Over and above important administrative considerations, the critique centred on the prematurity of the attempt. The attempt was made without evidence that beta-globin genes, so introduced into human bone marrow cells, would produce globin at any levels that would help patients. Evidence was also lacking to support the idea that viral thymidine kinase would give human cells a proliferative advantage. That genetically transformed cells can be successfully reestablished in human bone marrow have also been untested.

Accurate and verified answers to presently unresolved questions about the control and regulation of gene expression, already cited as the greatest challenge since the double helix, would seem to be a critical and necessary requirement for responsible attempts at human genetic therapy. It is worth remembering, as Bob Williamson stated, that:

> . . . we do not yet have the answer to the crucial question of whether it will be possible to restore correct control over the introduced genes, for it is absolutely essential that they should be expressed under the same controls as those in normal animals. Expression in inappropriate tissue or abnormal control in the cell in which they are normally expressed could be disastrous. A surplus of one globin chain would be as harmful physiologically as a deficit, substituting an iatrogenic illness for a genetic one.[62]

The criticism of this experiment, as well as considerations raised in its justification, identify several broader issues, discussed in the following sections of this chapter.

Toward Genetic Therapy?

Genetic Disease

More than 3 000 human diseases are known to result from hereditary defects. Discoveries of such diseases occur each year. The prevalence and social burden varies from disease to disease. In all cases, however, the afflicted individuals bear the terrible sufferings of physical pain and handicap, mental disability, or early death. Many persons suffer all three.

A massive burden of illness, presently incurable and often untreatable in effective ways, is the cumulative result of these hereditary disorders. They are "fast becoming recognized among the most important health care problems in the world today."[63] Though the genetic diseases are not intrinsically or essentially incurable or untreatable, "the currently available arsenal of weapons for attacking them is effective in relatively few cases."[64]

Hereditary disorders may be due to large-scale chromosomal defects. A person may have only one chromosome instead of two in a given group. In other cases, the afflicted person has one chromosome too many in a group. Down's syndrome, popularly called mongolism, is an example.

In other disorders, many genes, though not an entire chromosome, are the cause of the genetic disease. These are called polygenic diseases. Diseases due to single-gene defects are called monogenic.

Gene products – such as enzymes, hormones, and other proteins – are essential for life and human health. Single-gene defects, for example, frequently result in the human body's deficient production of these substances. When single-gene defects cause an enzyme deficiency, human metabolism may be seriously disrupted. The consequences are usually devastating and often fatal.

Therapeutic Approaches

Several therapies, short of replacing or correcting the defective genes, have been tried for these diseases.[65]

Control of the physical environment is essential, even if burdensome, for some genetic diseases. Persons afflicted with xeroderma pigmentosum lack an enzyme required to repair damage caused by ultraviolet light to the DNA of skin cells. These persons have to avoid ultraviolet light. Germ-free environments have been constructed for some children suffering from agammaglobulinemia, a disease linked to the X chromosome. Children with this disorder are afflicted with recurrent bacterial infections as they lose their maternal antibodies.[66]

Surgery in certain cases can stave off the fatal consequences of a disease resulting from gene defects. Children suffering from retinoblastoma develop malignant tuors in the retina of the eyes. Early surgical removal of the eyes can stop the spread of the cancer and permit survival.[67]

Dietary therapy has been successfully used for patients suffering from galactosemia and phenylketonuria (PKU). The strategy is to reduce patient intake of lactose and phenylalanine, respectively. These substances would otherwise accumulate in the body, because of a gene defect resulting in a missing enzyme, and cause mental retardation and death.

Drug therapy works at a later stage than dietary therapy in disruptions of the metabolic process caused by gene defects. The strategy is similar to that of dietary therapy: to reduce or block the build-up of harmful substances in the body. The drug allopurionol, for example, has been used to restrain the activity of the enzyme xanthine oxidase and to reduce the accumulation of uric acid in patients with Lesch-Nyhan syndrome.[68]

Enzyme replacement therapy has been attempted for several enzyme deficiency diseases caused by defective genes. The patient with Fabry's disease and lacking a hydrolase enzyme offers an example. The accumulation of a lipid in various tissues can cause death from kidney malfunction or cardiovascular disease. Injection of the missing hydrolase enzyme can reduce the lipid, but the enzyme itself is rapidly degraded after injection. This rapid disappearance is a general problem restricting the efficacy of enzyme replacement therapy.[69]

Bone marrow replacement or transplantation has been considered for some of the hereditary blood diseases, such as the thalassemias. None of the methods, however, offers a cure. Some of the treatments are burdensome, and the beneficial results are, in most instances, severely limited. "These limitations of current therapy," stated Friedmann and Roblin, "are stimulating attempts to develop techniques for treating human genetic diseases at the genetic level, the site of the primary defect."[70]

Genetic Therapy

Genetic therapy would involve gene transfer, which is the introduction and stable integration of a normal gene into chromosomal DNA to replace a missing or defective gene. Roblin has outlined the specific steps that would have to be achieved for a genetically therapeutic modification of human cells. The technical requirements would be:

> (1) isolation of specific sequences of human DNA coding for the desired genetic function;
> (2) integration of the added, exogenous human DNA into the chromosomal DNA of the recipient cells;
> (3) correct transcription of the newly introduced genes into messenger RNA (mRNA) and
> (4) the correct translation of this mRNA into protein in the cytoplasm of the recipient cell.[71]

W. French Anderson and John C. Fletcher have identified the necessary conditions that would have to be fulfilled for each gene replacement before an ethically justifiable attempt at genetic therapy could be undertaken in human beings. The fulfilment of these conditions require extensive prior animal experimentation and would not guarantee an effective, verified therapy. Extensive additional trials would be required for that kind of guarantee. The Anderson-Fletcher conditions are:

> First of all, the new gene shoud be put into the proper target cells and should remain there. If, however, the gene also enters other cells, it should be shown that the presence of the gene or its product does not damage the non-target cells.
>
> Secondly, the new gene should be regulated appropriately in the target cells. In other words, the gene's product should be made in amounts that are sufficient to correct the genetic defect but not so large as to have a detrimental effect.
>
> Thirdly, the presence of the new gene (and all other DNA sequences associated with it) should not

> harm the cell. Specifically, the inserted genetic material should not produce mutagenic events in the organism, interfere with regulatory pathways within the cell, or otherwise adversely affect critical cell functions.[72]

A great deal of additional knowledge has to be obtained and a set of technical skills has to be developed before these conditions can be fulfilled. Formidable difficulties must be overcome before an effective genetic therapy will be available for even one of the monogenic diseases. Moreover, a successful genetic therapy for one monogenic disease will not, in general, be transferable to or applicable for another monogenic disease. The accumulated knowledge and experience sufficient to develop one successful genetic therapy would, of course, make the achievement of other successful genetic therapies more likely. It should be emphasized that effective genetic therapies for monogenic diseases "would be totally ineffective against disorders caused by chromosomal aberrations or for polygenic traits."[73]

In 1970, Bernard Davis warned: "Education on the distinction between monogenic and polygenic inheritance is clearly important if the public is to distinguish between realistic and wild projections for future developments in genetic intervention in man."[74] Although genetic therapy for chromosomal abnormalities and for polygenic diseases is surely a great distance away, genetists are much closer now than they were in the early 1970s to an effective therapy at least for monogenic diseases. The first effective genetic therapy for a monogenic disease will most likely be achieved for a disease involving genes that have been extensively studied and defects that are biochemically well understood.

It is important to realize that a genetic therapy would not necessarily entail the introduction of a normal gene into the deficient cells of the tissue affected. One study indicated an alternative approach to the introduction of a normal beta-globin gene as a possible genetic therapy for beta-thalassemia.[75] The approach to be taken to develop a genetic therapy for beta-thalassemia, and for other monogenic diseases as well, will depend on the precise nature of the gene defect. More than one kind of genetic defect or mutation may produce the beta-thalassemia disease. These defects would include "structural gene deletions, nucleotide substitutions in the intervening sequences that cause abnormal mRNA processing, and nonsense mutations in the coding region that lead to premature termination of globin chain production."[76]

The proposed alternative to a genetic therapy for beta-thalassemia would apply when the disease is due to nonsense mutations. The approach entails the insertion of special genes, called tRNA genes, that suppress the nonsense mutation responsible for the premature termination of globin production in patients suffering from that form of beta-thalassemia. The investigators who developed this approach summarized its limits and advantages over beta-globin gene replacement as follows:

> Insertion of suppressor tRNA genes can be tested as an approach to gene therapy in beta-thalassaemia. While this approach would be limited to beta-thalassaemias due to nonsense mutations, it has a theoretical advantage over other proposed gene therapies for beta-thalassaemia, such as insertion of a normal beta-globin gene into thalassaemia cells. In experiments where a cloned beta-globin gene was inserted into heterologous cells, the level of beta-globin expression was low. At present, the mechanism that controls normal beta-globin gene expression is not understood. In contrast, since tRNA are essential for protein synthesis in all cells, inserted functional tRNA genes are likely to be expressed, even in differentiated cells such as erythroid cells.[77]

The use of retroviruses (viruses containing RNA rather than DNA) to transfer therapeutically needed genes into the appropriate cells of patients afflicted with a given genetic disease may prove to be one of the most promising approaches to genetic therapy in human beings. Scientists currently working with retroviruses are both cautious and optimistic about their potential as an instrument of genetic therapy in humans.

They are cautious because many important problems—such as the efficient transfer of therapeutically useful genes to the right target cells, the proper regulation of the proteins and enzymes these genes will produce, and the safety of such procedures—still require extensive experimentation. Medical scientists are also wary about raising unrealistic expectations. Most of the genetic diseases, particularly those caused by too much genetic substance rather than by the lack of a gene or the presence of a defective gene, will not be treatable by methods using the retrovirus as a transfer vehicle. Some genetic diseases, such as the hereditary blood diseases, sickle-cell anemia, and thalassemia, that would be appropriate targets for the retrovirus transfer of missing genes, such as beta-globin genes, present a major problem. The cure of these diseases would require that tansferred genes produce the correct amount of beta-globin. If retroviruses solve the problem of how to transfer genes, they are not likely to solve the problem of how to regulate properly the expression of these genes.

Nevertheless, there is cause for hope. Scientists appear to have solved the problem of constructing a retrovirus that will enter a cell, release the therapeutically desired genes, and otherwise leave the cell undisturbed. This method offers the greatest promise for an eventual attempt at genetic therapies that will not depend upon a precise location in the body or a precise regulation of the expression of transferred genes. For these reasons, some believe that Lesch-Nyhan syndrome and adenosine deaminase deficiency may be the first test cases for genetic therapy.[78] Lesch-Nyhan syndrome leads to mental retardation, cerebral palsy, and bizarre self-mutilating behaviour. Adenosine deaminase deficiency is a serious disorder of the body's immunological defence system.

Genetic Therapy: Points of Consensus

Can gene therapy be done? In 1980, Bob Williamson answered: "At the moment, the answer is *unequivocally* no. This is an extremely important point; no gene replacement that is meaningful in the context of human genetic disease has yet been achieved even in model systems with animals."[79] In 1986, one would have to answer more cautiously. The first experimental attempts at gene therapy in humans might be undertaken before the end of 1987. This prospect notwithstanding, some researchers would consider gene therapy impracticable now for two principal reasons. First, most inherited diseases affect several body tissues, not only one. Second, even in the case of a monogenic disease affecting one replaceable body tissue, such as bone marrow, medicine and science cannot yet ensure that genes implanted into the cells of such a tissue will function as required.

Scientists and doctors would generally agree that "ultimately gene therapy in human beings should be possible."[80] Moreover, most knowledgeable and responsible persons would agree that "gene therapy is a proper and logical part" of the biomedical research effort to alleviate human suffering.[81] Yet, any policy on gene therapy will have to take account of the distinction "between treatment of a serious disease in a way that affects only the patient himself, and treatment of an early embryo so that its inheritance is altered.[82]

The genetic diseases mentioned recently as the likely first test cases for genetic therapy are Lesch-Nyhan syndrome and adenosine deaminase deficiency. Earlier estimates that the hereditary blood diseases, such as sickle-cell anemia or beta-thalassemia, would be the targets of first attempts at genetic therapy have been revised. It is now recognized that the problem of how to regulate gene expression will have to be solved before attempting human genetic therapies for these diseases.

Those engaged in the study and practice of genetics generally agree that the development of effective genetic therapies for many of the monogenic diseases will depend upon major advances in understanding the mechanisms that control normal gene expression. Genetic therapies for polygenic diseases and for disorders due to chromosomal abnormalities are not expected for a long time.

The testing of potential human genetic therapies in animals is both possible and necessary before attempts can be made with human beings. Most geneticists believe that before trying genetic corrections of hereditary defects in human beings, it is essential "to learn how to correct defective cells not in a laboratory culture but in genetically defective experimental animals."[83] It should be possible to develop animal models of several human monogenic diseases, given the recent generation of lines of mice that have alpha-thalassemia. Any advance toward genetic therapies will be more respectful of the dignity and clinical needs of human beings and "no less impressive if preceded by a few more small steps for a mouse."[84] Premature attempts at genetic therapy in human beings, attempts not based on a thorough examination "for efficacy and freedom from short and long term side effects"[85] – could well discredit this line of biomedical research in the eyes of the general public. The ethical guidelines, established in recent years for clinical trials and for experimentation with human subjects, apply to the development of genetic therapies and any innovative therapeutic regimen.

Some scientists are concerned that genetic therapies, when they become available, might be impractical. Cost effectiveness of genetic therapies compared with other available treatments, even if less profound, is the issue. The raising of "false hopes of a molecular 'cure' among those with genetic diseases" is the more human side of this concern.[86] The point upon which reasonable people might well agree is that the economics of potential genetic therapies should be carefully analyzed, not only their scientific and medical validity.

Continuing advances in molecular biology and genetics will exert a major effect on medicine and medical education. Within the scientific community, Paul Berg would find considerable support for his view that:

> Such detailed information has profound implications for the future of medicine. Just as our present knowledge and practice of medicine relies on a sophisticated knowledge of human anatomy, physiology, and biochemistry, so will dealing with disease in the future demand a detailed understanding of the molecular anatomy, physiology, and biochemistry, so will dealing with disease in the future demand a detailed understanding of the molecular anatomy, physiology, and biochemistry of the human genome.[87]

Genetic Engineering and Genetic Therapy: Concerns, Uncertainties, Controversies

Some of the early issues that dominated the recombinant DNA debate have quieted and given way to uncertainties and nascent controversies of a quite different kind. Concern for public safety, the fear of biohazard, clashes about the kinds of containment needed for various kinds of recombinant DNA experiments and debate about the stringency of regulation required for public protection no longer dominate public discourse on innovations in genetics and molecular biology. The following sections identify some of the major shifts of emphasis in the evolving public discourse on the new genetics as the industrial, pharmaceutical, and medical possibilities opened up by recombinant DNA technology come closer to realization.

Genetic Engineering of Future Generations

Two fundamentally different and often conflicting perspectives are possible for any event: that of persons involved in what is happening and that of those on the outside. After the development of recombinant DNA, scientists claimed that molecular biology without doubt "now had the power to alter life on a scale never before thought possible by serious scientists."[88] Many outside and some within the scientific community reacted with little enthusiasm to the development of such power. As H. Vasken Aposhian warned in 1970, "The term 'genetic engineering' has the revolting connotation to many of impersonal scientific manipulation of the future of human life and offends the dignity of many."[89]

On the opening evening of a forum on recombinant DNA, organized by the National Academy of Sciences in March 1977, Jeremy Rifkin, spokesman for the People's Business Commission, attacked the question of the central issue in the recombinant DNA debate:

> My friends, the real issue is not whether the laboratory conditions are safe or unsafe, although obviously there is a problem with potential viruses and bacteria getting out of the laboratory and endangering the health and well-being of millions of people. But that is not the central issue. . . .
>
> The real issue here is the most important one that mankind has ever had to grapple with. You know it, and I know it. With the discovery of recombinant DNA scientists have unlocked the mystery of life itself. It is now only a matter of time – five years, fifteen years, twenty-five years, thirty years – until the biologists, some of whom are in this room, will be able literally, through recombinant DNA research, to create new plants, new strains of animals, and even genetically alter the human being on this earth. Some scientists in attendance will say this is sensationalism, this is emotionalism. Well, it is because this technology is sensational, and because it hits right to the basic emotional core of life itself. For three generations of Americans weaned on Huxley's *Brave New World* the long range implications of experimentation in this field are ominous.[90]

David Dickson reported in *Nature* that, at a meeting in 1981, the U.S. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research suggested "the establishment of a new body – possibly at an international level – charged to seek a social consensus on the various dilemmas which the expanding clinical use of genetic engineering techniques will raise."[91] The commission members seemed to agree that coming applications of genetic engineering could well exercise profound effects on society, "for example in terms of the potential ability of an individual to alter the genetic characteristics of his or her descendants."[92]

Nature reported in February 1982 "a move to widen the scope of the European Human Rights Convention to include the dangers of genetic engineering."[93] According to this report, the legislators at Strasbourg are proposing that the convention include "the right to a genetic inheritance free from any form of engineering."[94] A more recent article in *Nature* quotes a recommendation of the Council of Europe requesting provision "for explicit recognition in the European Human Rights Convention of the right to a genetic inheritance which has not been artificially interfered with, except in accordance with certain principles which are recognized as being fully compatible with respect for human rights. . . ."[95]

These proposals illustrate the fear that molecular biologists are developing a technology that will one day deliver the power to tinker genetically with the inner nature of human beings and to manipulate future generations for eugenic purposes. Statements such as that of Rifkin express in lay terms the anxieties and fears that many share about the rise of a powerful, scientifically knowledgeable elite, technically able to tamper with life at its origins.

Are these anxieties and prospects at all proportionate to the real agendas and capacities of contemporary molecular biology? Will these feared engineerings of future generations ever be achievable?

The answer of most scientists is quite definite. Most would emphasize that the scientific knowledge and the technical ability genetically to "alter people against their will"[96] is beyond present and even distant horizons. One writer's opinion is categorical:

> When we come to such vague concepts as "aggression" or "intelligence" or "good looks," we are off in the land of the fairies. If there are any inherited determinants for these attributes, we are so far from understanding, isolating or measuring them that it is barely worthwhile even considering that an attempt at gene therapy could be made with any prospect of success.[97]

Earlier discussion showed that scientists are only beginning to understand single-gene defects and that genetic therapy for even one of the diseases resulting from such defects is not yet practicable. They are surely many years away – some would insist light-years away – from being able to make a genetic blueprint and to engineer complex behavioural traits. Anderson and Fletcher have described how much remains unknown:

> Intelligence, personality, fertility, organ structure, and physical, mental, and emotional characteristics are all presumably controlled or influenced by vast arrays of genes about which we know little or nothing. There are dozens, maybe hundreds, of genes within every cell that make regulatory substances used by the

> cell in unknown ways. We do not know what the substances are, how they work, or what genes are involved. Any planned alteration of multigenic traits will not be accomplished by gene therapy for many decades to come, if ever.[98]

Should these assurances be trusted? After the public row over recombinant DNA, some may wonder whether scientists, motivated by the fear of a public backlash and of a demand for increased public involvement in the regulation of scientific research, are unwittingly softening their estimates of the momentum of scientific advance toward a full understanding of the genetic workings of human life. Are scientists interested in distracting public attention from an inexorable scientific trend toward the knowledge and technology that will one day permit effective genetic manipulations of human beings and of future generations?

Even if the answers to these questions were to be a resounding no, may science, in fact, not advance much more rapidly than some predict? A 1982 report described the successful genetic modification of eye colour in fruit flies, a complex multi-celled organism.[99] This genetic modification changed the eye colour of later generations of these flies, not only of the embryos that were the immediate target of the experiment. Would scientists in 1977 have predicted this achievement for 1982?

Scientists' opinions today about the timetable for achieving the scientific knowledge and technical competence needed to modify important human characteristics genetically should be seen as solid and beyond reasonable doubt. These powers do, indeed, lie in the distant future. If science is moving steadily toward the development of such power, however, can those responsible for the common good afford simply to sit back, wait, and see? Should the length and diligence of our preparation not be measured by the magnitude of the power our great-grandchildren will have to face?

Results of Recent Research: Toward Genetic Experimentation on the Human Embryo?

Are scientists heading toward genetic experimentation on the human embryo? The question is reasonable when one glances at the progressively higher life forms chosen for experiments in genetic engineering since the early 1970s. Within a few years scientists advanced from recombinant DNA experiments on bacterial cells to the micro-injection of specific genes into human and animal cells maintained outside the body in tissue culture.

Since 1980, a cluster of experiments have successively introduced foreign genes into the fertilized eggs of frogs and mice. The genetically modified mouse embryos, when mature and mated, produced offspring that were also genetically modified. These experiments offer the basis for more profound and productive studies of two large unknowns: the control of normal gene expression during an animal's development and growth and the causes and possible cures of genetic diesases.[100]

It is now possible with methods of in vitro fertilization to create human embryos in the laboratory. In the experiments cited above, the researchers viewed fertilized frog and mouse eggs as "assay systems," permitting the study of gene expression during cell differentiation and development. Is it not likely that investigators will view the early human embryo as an assay system to study human gene expression during embryological development?

Before determining the conditions under which genetic experimentation with the human embryo should be permitted, if at all, one should know whether such experimentation is practicable or useful. The jump from gene transfer experiments on mice to the conclusion that scientists are gearing up to initiate similar experiments on the human embryo may be unjustified. Are current or later generations of scientific questions likely to arise that will call for information unobtainable from animal experimentation? How likely is it that gene transfer experiments on the human embryo would be the approach required to answer these questions? The human embryo has a long gestational period in comparison with the mouse. Would gene transfer experiments on the human embryo be at all worthwhile? Short of a system capable of supporting the development of the human embryo outside the mother's body, would scientists not have to wait nine months at least for answers to their questions? What sorts of continuing experimentation on the newborn child would then be necessary to complete the experiments initiated on the human embryo?

Scientists generally deny that there is any current intention of initiating genetic experimentation on the human embryo. In fact, it seems unlikely that there is any scientific justification for undertaking gene transfer experiments on the human embryo now. But will that still be the case tomorrow? When sufficient progress has been made, will scientists not need to turn to the human embryo to make further progress in understanding gene expression as well as the causes and possible cures of genetic disease?

Gene Therapy: Possible, but Realistic?

Some people may harbour the seductively simple and false idea that gene therapy, when perfected, will be easily applicable through tablets, capsules, or injections. Others may identify "genetic surgery" with the routine or highly complex operations they have either experienced or seen in films and television programs. In fact, genetic therapy, even after likely future successes for some single-gene diseases, will continue to be something quite different from the familiar treatments of modern medicine.

If public policy is influenced by public expectations, it is important that these expectations be realistic. Genetic therapy may soon be effective for single-gene defects affecting a body tissue, such as blood and bone marrow, that can be removed, treated, reimplanted, or transplanted.

The story is altogether different, however, for single-gene defects affecting several different organs and tissues. Cystic fibrosis, a fairly common single-gene defect, is an example of a genetically based disease affecting several organs and tissues of the human body. Even with advances in transplant technology, it will remain so difficult to remove such tissues for gene implantation that genetic therapy for such diseases will probably be unrealistic for a very long time. It is even more unrealistic to expect gene therapies for diseases resulting from the combined causality of many genes and environmental factors.

Some will ask, why wait until childhood or adulthood to undertake genetic therapy? Is it not more realistic to undertake genetic surgery on the early embryo when there are only a limited number of cells, rather than fully developed organs and tissues? This approach presumes that a couple knows of its genetic risk, is ready to conceive a child via in vitro fertilization, and is prepared to undergo the risk of failure of the embryo transfer after all the efforts at genetic surgery have been made on the embryo.

The medical and scientific professions are committed to finding cures and treatments for diseases that can be diagnosed. Society is already accustomed, however, to the abortion of genetically defective fetuses after prenatal diagnosis of fetal abnormality. Will parents generally be prepared to go through all the trouble and uncertainty of attempts at genetic therapy on their early embryo when very early detection of defects and very early abortion will exist as competitive alternatives?

Other trends in our society also have to be considered. After Dr. A.W. Lilley's pioneering treatment of the fetus by intra-abdominal infusion of blood in the early 1960s, doctors have, at least since 1980, successfully treated or operated upon fetuses while they were still in their mothers' wombs. Will an expanding perception of the fetus as a patient affect North American Society's ethics of abortion? If genetic therapy on the embryo becomes feasible, will the medical community and society come to view the embryo as a patient?

These reflections are based on current knowledge and experience. It is likely that science will advance in perfecting the skills required for gene therapy, specially for single-gene defects. It is too early for reliable predictions on the fate of genetic therapies after initial future successes. As Paul Berg observed, one thing, however, is certain: "Gene therapy will have to be evaluated in terms of alternative and more conventional forms of treatment, just as is now done before undertaking heart value replacements and renal transplants."[101]

Standards of Medical Practice versus Individual Patient Welfare

Gene replacement therapy for monogenic hereditary diseases may raise an ethical dilemma and become a public policy issue before modification of the human germ line does. The issue has already appeared in Dr. Martin Cline's attempt at genetic therapy on two young women suffering from beta-thalassemia (described in detail in the above subsection "Genetic engineering in the adult human body."). A conflict between responsibility to public medical standards and responsibility to individual patient welfare may be at stake. Although in theory there should be no conflict, in practice there may be. Patients suffering from terminal illness with short life expectancy may well be ethically justified in requesting and submitting themselves to a highly experimental, untested procedure. After long efforts significant advances have, however, been made in establishing reasonable ethical conditions for human experimentation and for the use of unverified therapies. What guidance could these principles offer if continual exceptions were to undermine their credibility?

This was the thrust of one criticism leveled against the Cline experiment: "Just because Pasteur, Jenner, and others succeeded in their approach doesn't mean that scientists should continue in that same way. Science has evolved with procedures for human experimentation to protect humans from unsound experiments."[102]

Dr. Cline has presented a counterview based on two considerations about beta-thalassemic patients with limited life expectancy:

> Is it premature to consider Phase I studies of gene insertion in such patients if these studies hold even a small chance of success? ... Since study of delivery systems and toxicity will take a very long time, a careful Phase I trial based on promising animal data seems a reasonable place to start. To delay beyond the point of reasonable prudence means that an undetermined number of patients will die who might have been saved if the crucial advances had come sooner.[103]

As early as 1972, Richard Roblin had asked, "Since the physician concerned may also be active in trying to develop the gene therapy technique, how can the patient be protected from a physician who might be overeager to try out his new procedure?"[104] Hospital and institutional committees in the future will likely hold to the standard of medical ethics that condemned Dr. Cline's attempt as being premature. According to the standard that using patients, however ill they may be, as laboratory animals is against the fundamental canons of humanism, Dr. Cline's experiment may well have merited the following even stronger judgment of Bob Williamson:

> Cline's experiments were fundamentally unethical. His own work on mice showed that there was no basis for hope the globin gene insertion into marrow cells could give clinical benefit at that time. The thalassaemic patients were irradiated at a high level to clear the marrow in the long bone of one leg, a procedure of some risk, and they and their families were given hope that the gene therapy might help them in their fight for survival. It is unacceptable that patients should be misled in this way, and certainly makes it more difficult for medical research workers to argue that our house is in order ethically.[105]

Engineered Forms of Life: Patents and Ownership

Genetic engineering became the centre of issues dealing with the patenting of life forms when the U.S. Supreme Court, in June 1980, issued its decision in the case of *Diamond* v. *Chakrabarty*. The case turned on an application filed by A.N. Chakrabarty in

1972 to patent a novel strain of the bacterium *Pseudommonas aeruginosa*. Chakrabarty, using conventional genetic manipulations, not recombinant DNA methods, had modified this bacterium to produce an oil digesting microbe. The application claimed patent protection for the method of producing the bacterium, for the process of applying the bacterium to an oil spill, and for the bacterium itself.[106] The Patent and Trademark Office, subsequently upheld by its Board of Appeals, rejected the claim to patent protection for the bacterium itself.

The issue at stake was whether the result of a genetic rearrangement or modification of living matter could qualify as a manufactured product. The Supreme Court answered in the affirmative, holding that the life form resulting from genetic or other manipulations is identifiably a human invention and not a product of nature.

Some interpreted this decision as an assault on the sanctity of life. Others raised the question where the limits to patent ownership of genetically engineered life forms could be set and on what basis. The question may become very practical and demand greater clarification than that offered by the U.S. Supreme Court if "the genetic manipulation of agriculturally important animals" quickly follows recent successful genetic engineerings of mammalian embryos.[107] The question about the status of life forms may generate even more intense controversy if genetic engineering is ever used to modify the human embryo.

The Human Germ Line

Most current discussions of future gene therapy emphasize the distinction "between treatment of a serious disease in a way that affects only the patient himself, and treatment of an early embryo so that its inheritance is altered."[108] Experiments already mentioned in this study have modified later generations of mice by micro-injection of foreign genes that entered the mouse embryo germ cells. In a more recent experiment scientists have succeeded in transferring DNA segments for eye colour into the germ line of fruit fly embryos resulting in stable inheritance in later generations.[109]

These scientific achievements weaken the speculative character of the question about the justifiability of ever attempting similar experiments on the human embryo that could result in the modification of future generations of human beings. The question stands even if initial modifications were to be relatively insignificant when compared with a human being's full behavioural repertoire. In 1970, Bernard Davis expressed the following view:

> If predictable genetic alteration of germ cells should become possible it would be even more useful than somatic cure of monogenic diseases, for it could allow an individual with a defective gene to generate his own progeny without condemning them to inherit that gene. Moreover, there would be a long-term evolutionary advantage, since not only the immediate product of the correction but also subsequent generations would be free of the disease.[110]

Curing a disease once and for all would seem to be so much more effective than having to repeat a cure in each generation. The very concept, however, is already controversial. Richard Novick, for example, has taken a quite definite stand, asserting that he "would have no difficulty in supporting specific gene therapy while rigidly interdicting any intervention in the germ line, including attempts at correcting specific diseases, as well as open-ended 'eugenic' manipulation even long before it becomes technically possible."[111]

The planned genetic modification of human inheritance, that is future generations, seems to be a Rubicon many believe should never be crossed. Does this belief rest on the fear that once scientists do cross that line, they shall be irrevocably bound to attempt ever more grandiose projects of future human design?

During the debate on recombinant DNA, Robert Sinsheimer asked a question considered by many to be far ahead of its time, a time that may now be approaching. "How far," he said, "will we want to develop genetic engineering? Do we want to assume the basic responsibility for life on this planet – to develop new living forms for our own purpose? Shall we take into our own hands our own future evolution?"[112] To have asked this question early and to ask it frequently may well show more wisdom than to pretend it should not be asked at all.

Conclusion: The Relationship of a Free Society to Its Scientific Community

In fifteen turbulent years, the work of molecular biologists has brought us to the frontier of genetic therapy for monogenic disease. How a free society relates to its scientific community is undoubtedly the broader issue emerging from the controversies of this period. The issue is "the legitimate role of the public and their legislative representatives in deciding the direction of scientific research and the utilization of scientific knowledge."[113]

There is some truth in the view that science directs itself as it follows the internal logic of discovery, but that is surely not the whole truth. Science is carried by scientists, and the commercial prospects of recombinant DNA have shown that the external forces of financial gain and fame can exert an influence of their own.

There is some truth in the view that molecular genetics is so complex that only the scientists involved can sense and assess the directions that their science must follow. The weakness in this view, however, is that science does not exist for its own sake alone. It exists for the sake of mankind. Are the directions that mankind will take in a scientific age, a genetics age, to be determined by scientists alone?

The challenge in this view is that those without knowledge have little power. If the people have little power, a free society is weakened. The challenge became apparent during the debates and controversies of the recent past. Lay participation, at various institutional levels, in the regulation of recombinant DNA research was an achievement. That participation, however, "has not bridged the enormous gap in knowledge between the scientists and the general public."[114] The challenge remains "to learn how ill-prepared scientists and the public still are to face the issues that confront them jointly and how to improve their relations while there is time."[115]

Chapter 4:

Comprehensive Issues

David J. Roy
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Introduction

The three preceding chapters of this study have identified public policy issues specific to each of the technologies under examination. The need for a legal definition of motherhood, acute today in the practice of surrogate motherhood, is not an issue in prenatal diagnosis and genetic engineering. The question of risk and the need for regulation, although also relevant to prenatal diagnosis and the reproductive technologies, assumed great importance in the life sciences with the rise of recombinant DNA technology.

The term "issue" has been used throughout this study to cover needs, questions and problems for which answers or solutions are either conflicting or inadequate. Issues characteristically generate debate. They rarely can be resolved to the total satisfaction of the contending parties. Some issues, under the pressure of time and change, disappear from the public forum; others divide the community deeply until they are resolved. Some of the issues in this latter group are intractable. The challenge for those responsible to the public is to devise policies that enable divided groups to continue working and living together.

In the course of this study, issues not exclusive to any single technology under examination have recurred as each of the technologies was explored. These issues are called comprehensive because each technology in varying ways reinforces its emergence as a target for societal discourse. They are comprehensive also in a sense that identifies what is meant by a "public policy issue." Issues of this kind cannot be resolved by government alone or by a single professional community. They are among the concerns that require the attention of each of the estates of Canadian society: local, provincial, and federal government; the scientific community; industry and business; the media; the academy; the religious communities; and the professions, especially medicine and law.

This concluding chapter identifies and opens a discussion of several of these dominant, comprehensive issues arising from recent developments in the life sciences. A technology-related issue is defined here as dominant when:

- it has generated a sizeable volume of literature
- it involves important values as contrasted with peripheral interests
- it affects the common good and the achievement of the public purpose
- it manifests a conflict of perceptions on activities that are essential to the harmonious development of society; for example, human reproduction, education, medicine, science
- it makes claims on a significant segment of public resources
- it cannot be resolved without the collaboration of specialists in diverse fields with persons at various levels of public responsibility

Conflict of Perceptions

Each of the subjects examined in this study documents conflicts of perspective, horizon, and perception. These conflicts shape the matrix out of which public policy arises and the context within which public policy must operate. The opposition is not static, as the images expressing these opposing views motivate, inspire, arouse, and mobilize people. They generate opposing courses of action on concrete matters that affect everyday living as well as professional activity. The conflicting images build groups of allegiance, and the dialectic of ideas and perceptions fast becomes a social dialectic. A potentially healthy tension that promotes growth within a community, however, also runs the risk of settling into a paralyzing polarization. These divergent views give rise to five kinds of conflict.

One kind can be settled by fresh data or by an accumulation of evidence or experience that supports one view, shows others to be exaggerated, and eliminates still others from serious discourse.

Years of experience with artificial donor insemination, for example, have produced no evidence that this approach to human reproduction produced greater psychological stress on couples or greater distortion of the psycho-social development of the child than can be documented in families using natural insemination.

Years of experience with many safe recombinant DNA experiments have substituted a base of assurance for the uncertainty and sharply polarized views on hazards that existed during the early debate on recombinant DNA.

For conflicts of this type, the lesson for policy makers should be obvious. When the social consequences are uncertain, new developments need a trial run until a sufficient accumulation of experience reveals the limits and protections that have to be established.

A second type of conflict arises because, like the blind men in the fable touching different parts of the elephant, persons with only a partial experience make judgments on the whole. Conflicting judgments that can arise from limited experiences are not necessarily intractably opposed. A synthesis of the partial experiences may cause these conflicts to diminish or even to disappear. Achieving the synthesis, of course, presupposes the realization that no human mind or specialist community has a monopoly on knowledge, interests, or values.

Third, a conflict of perceptions may arise because one or more views are out of phase with the way things really are. The effects of scientific research, for example, are now quickly felt outside the realm of pure theory. The goal of science is to understand the nature of things, that of technology, to change the state of things. The lag time between the two is, however, very short. The view emphasizing the freedom of scientific inquiry from outside interference can no longer rest on outdated claims about the theoretical purity and practical innocence of scientific achievement. The closer science moves to the power to change things, the more surely will demands arise for public participation in negotiating how that power will be used.

A fourth kind of conflict arises from a restricted focus on one value. During the debate on recombinant DNA, some scientists were concerned that the debate was proceeding in a manner detrimental to the scientific enterprise as a whole. Others feared that the way science was proceeding could be detrimental to mankind as a whole and, specifically, to future generations. Restricted focusing on one value causes the other to appear as a threat. The inability to appreciate each value creates bias in favour of one or the other. The objective is to achieve a balanced commitment to different values.

This objective raises a question: How can a balanced commitment to different values be attained in a society increasingly fragmented into specialist communities? Scientists are not trained to think critically about social matters. Social scientists and humanists are overwhelmed by the complexity of modern scientific technology. The public at large is generally unable to keep step either with science and technology or with the complicated effects of both on society.

Fifth, conflicts that appear intolerant of any resolution are the most difficult to handle. There is no substitute in an open society for compromise, tolerance, and the long process of civilized argument and persuasion in the face of conflicts on major issues that cannot be readily resolved. The dominant view may win legal support, for a limited period of time. If that view is fundamentally flawed, however, the give and take of critical debate will eventually bring about its reversal. The challenge to public policy is to foster and maintain the ongoing process of communication necessary for an eventual adjudication of conflicts that divide a society.

Communication and Public Education

Few would disagree with popular broadcaster David Suzuki's assertion that it is "science, when applied by industry, by medicine, by the military that has by far the most impact on society."[1]

When consumers, who demand a technology, and policy makers, who regulate its introduction into society, fail to achieve more than a superficial understanding of the scientific technology, they invite chaos. An alternative in a society dominated by complex technologies is the possibility of government by a small circle of the scientific and technological elite. Robert Sinsheimer has seen this possibility as one of two newly emerging threats to individual liberty:

> Traditionally we have thought of freedom as the protection of the individual from the far greater powers of the state. We have gradually generalized that concept to protection from the great economic power available to large corporate enterprise. We need today to consider two newly emergent threats to individual liberty.
>
> One arises from the power that modern science may give to a small group ... to threaten an entire society, and from the societal controls that such capability may call forth. The other arises from the ever-increasing connectivity and interaction of our society and the power thus afforded to those who ... find the unplanned control points in such a society and thereby direct its evolution.[2]

Instead of a democracy, a technological aristocracy with mastery of the complex technologies needed to shift society at the points of maximum control may be a social possibility. It may not yet, however, be the only reasonable alternative.

The maintenance of community is a fragile human achievement that calls for effective, ongoing communication. Bernard Lonergan has described the community and the results of a failure to communicate:

> Community is not just an aggregate of individuals within a frontier, for that overlooks its formal constituent, which is common meaning. Such common meaning calls for a common field of experience and, when that is lacking, people get out of touch. It calls for common or complementary ways of understanding and, when they are lacking, people begin to misunderstand, to distrust, to suspect, to fear, to resort to violence. It calls for common judgments and, when they are lacking, people reside in different worlds. It calls for common values, goals, policies and, when they are lacking, people operate at cross-purposes.[3]

It is difficult to achieve the kind of communication needed to maintain community in a complex technological society. New knowledge and technology are snowballing, and are becoming ever more specialized and complex. Such a society needs information that is accurate, up to date, integrated, continuous, easily accessible, and intelligible not only for its decision makers, policy designers, and educators but also the general public.

It is largely true that "the press is the medium through which the public gets much of its information about science and science policy."[4] Does this medium, as it presently functions, meet the needs of those requiring the information? Because "the press is largely a reactive institution," the information needs of a society making rapid scientific and technological advances may well call for a communications bridge between science and technology, on one side, and the media, on the other.[5] An "Institute for Integrated Scientific Communication," beholden only to the people, could be this bridge.

Such an institute could correct the fragmented, sporadic, exaggerated, and reactive character of much of the scientific information people receive today. It would have a mandate to examine the advances in specialized branches of science and technology and to prepare documentaries for diverse audiences. This mandate suggests the type of staff that would be required.

Such an institute would need the ongoing collaboration of media and science experts. The success of its work would assume and require a heightened sense of responsibility on the part of scientists and the creators of new technologies, to adequately inform the public, who in large measure provide the funds for their work.

This issue is dominant for each of the subjects discussed in the chapters of this book. New biomedical developments with great power over human beings cause many people to fear that human identity, uniqueness, primacy, and safety are being threatened. These anxieties complicate the discussions of and policy decisions on nascent technologies. What Willard Gaylin has called the "Frankenstein Factor" then enters, and may for a while dominate, the public forum where the common good is negotiated.[6] Fear of the monster that may be created triggers an anti-science and anti-technology bias that, in direct proportion to its irrational and unconscious nature, distorts public debate and the negotiation of the common good.

An improved flow of information would allow the public to associate itself critically with the scientific and technological communities. The ability to use this information will increase if schools and universities emphasize the goal of preparing people not only to work in the world but also to understand the world in which they work.

Public Participation

One of the main issues emerging from the debate on recombinant DNA, an issue encompassing the other technologies discussed in this book as well, centres on the participation of the general public in determining the directions of scientific research and the applications of scientific knowledge. The Cambridge Experimentation Review Board, appointed by the City of Cambridge, Massachusetts, to consider questions of safety raised by recombinant DNA, took the position that "decisions regarding the appropriate course between the risks and benefits of potentially dangerous scientific inquiry must not be adjudicated within the inner circles of the scientific establishment."[7]

As seen in the debate on recombinant DNA, the scientific community frequently proceeds from quite a different assumption. The Asilomar Conference, praised as an unprecedented exercise of scientific responsibility, was simultaneously criticized for lacking public participation: "The Asilomar participants represented no constituency other than their colleagues and were not accountable to the broader scientific community or to the general public."[8]

Some members of the scientific establishment candidly expressed their intention not to go to the general public at the outset of discussions on recombinant DNA.

> "Although some fringe groups (such as Science for the People) thought this was a matter to be debated and decided by all and sundry, it was never the intention of those who might be called the Molecular Biology Establishment to take this issue to the general public to decide. The matter was not only too technical but in a way also too fuzzy for responsibility to be easily shared with outsiders. We did not want our experiments blocked by over confident lawyers, much less by self-appointed bioethicists with no inherent knowledge of, or interest in, our work. Their decisions could only be arbitrary."[9]

The issue of public participation in negotiations about scientific research and applied technology, whether through elected representatives or more directly, is multidimensional. Of the three central questions – whether, when, and how – the last is perhaps the most difficult to answer.

The government of the City of Cambridge answered the question "whether" by asserting its right to be involved in negotiations about the safety of experiments with recombinant DNA. Did the workings of its appointed Experimentation Review Board also offer one possible answer to the question "how"? This board was entirely composed of non-scientists. The members met several hours each week for four months and spent even more time doing homework to prepare for the meetings. In the end, the board recommended that research on recombinant DNA should continue, while suggesting broader public representation in university biohazard committees.

This board's decisions could not be characterized as arbitrary. Its performance supported the belief of its members "that a predominantly lay citizen group can face a technical scientific matter of general and deep public concern, educate itself appropriately to the task, and reach a fair decision."[10]

One may doubt whether the Cambridge "experiment on how a lay citizen group could participate in decisions concerning science" can be generalized.[11] This participation might be more effective if shared with scientists. Without scientific representation, lay citizen groups of the Cambridge type "are unlikely to win the confidence of the scientific community unless, as in the Cambridge case, they made a decision compatible with scientific interests."[12]

The mode of public participation in decisions about the directions of scientific research and applied technology will inevitably remain heavily conditioned by the styles of public discourse peculiar to each nation. The demand for public participation is not likely to be just a passing phenomenon. It may well represent the achievement of a higher level of consciousness about co-responsibility for science and technology. If that proves to be the case, the style of public discourse on science and technology will have to spawn the procedures and the forums appropriate to this new public consciousness.

The Corporate Connection

The potential profits from applications of recombinant DNA, monoclonal antibody technology, and other forms of microbial engineering are estimated to be enormous and imminent. Several industries show a marked interest in collaborating with university-based scientists to develop the potential of these technologies and to launch profitable commercial ventures. Individual scientists and some universities show the same interest.

An emerging connection between industrial and academic science is apparent in the grants from major industrial corporations for university research, in patents and patent licensing, and in the formation of private corporations in which the professor-scientists alone or the university also has a share. One commentator believes that "in the long run, the establishment of ties between academic institutions and industrial corporations, large and small, may turn out to be one of the more important 'scientific' developments of the 1980s."[13]

A new connection of societal institutions seems to be occurring. Professor-scientists, universities, and industrial corporations have worked together for years. The industrial-academic connection of the past seems, however, to have preserved the "species difference" of each. The new connection gives some evidence of being a "cultural recombination" that crosses "species barriers." The professor-scientist, while remaining within the university, is transformed into a entrepreneur, a key figure in a private corporation. An industrial corporation can hardly help being "expressed" within the university when it invests major sums of money in university research.

This emerging symbiosis has raised several serious questions:

- Can the professor-scientist-entrepreneur successfully honour a double ethos and respect a double ethics, that of the disinterested seeker of knowledge and of the highly interested entrepreneur?
- What effect will the marketing philosophy and mentality exert on the objectivity of the university-based research scientist?
- What effect will the attitude of business-competitiveness exert on the openness of communication that is essential for constructive criticism and real scientific advance?
- To what degree will society and the scientific community want the future directions of biomedical research to be determined by the industrial goals of marketability and profitablity?
- Present breakthroughs in molecular biology had to be prepared by many years of painstaking, financially unprofitable research. Will the industrial connection entice scientists away from basic research?
- If the publish or perish imperative has had detrimental effects on the quality of university teaching, what will happen if the patent or perish imperative becomes dominant?
- What effect will the corporate connection have on the society's opinion of scientists and the scientific community? Will public confidence in the expert opinion of scientists on the risks and benefits of a new technology diminish when scientists have a commercial interest in these same technologies?
- Does the corporate connection necessarily imply an abandonment of the principle that the results of publicly funded scientific research should promote public benefit rather than profit-making by either individual professor-scientists or the university?
- Is government funding sufficient today for the development of the kinds of projects that university-scientists find it necessary to pursue?

For those who believe this connection offers opportunities that are appropriate to the times in which we live, the issue is how this connection can be best arranged to protect academic ideals and simultaneously to exploit potentially explosive profits for the good of science, the university, and the general public.

Concerns about the present direction of university research have, in fact, motivated various schemes for establishing a university-industrial or a university-corporate connection.

Bernard Davis cites the increasing financial insecurity of universities today in the context of a monolithic dependence of university-based research on an often unsympathetic government.[14] In some cases, an efficient collaboration between a university and an industrial corporation may be the only way to bring the pharmaceutical, medical, and agricultural benefits of new developments rapidly within reach of the general public. This perspective emphasizes that massive governmental funding has meant governmental control of the directions of research. The effects on the internal logic of science of this external logic of "the public interest" is probably no less distorting than a market logic would be.

Any resolution of this issue will have to balance the concerns expressed in the two following, quite different points of view. Sheldon Krimsky writes:

> The direction of research influenced by industry may not be the direction that is in the public interest. Corporate requirements for scientific research may be at odds with pressing societal needs.
>
> Our academic institutions and academic scientists need to be free from corporate influence. And such influence can emerge in various ways: through direct funding by corporations to departments and investigators, by scientists serving as consultants to or on advisory boards of industrial firms, or by academic scientists playing a double role by setting up their own small venture-capital firms. . . .
>
> These are dangerous moves if they become widespread because in the end university-based science will lose its sense of detachment.[15]

Bernard Davis counters:

> We may all regret the loss of the more Arcadian atmosphere of the past. However, if universities are to protect their financial base in order to advance their academic goals, nostalgia will be no substitute for imaginative adaptations and a tough-minded attitude. There are surely risks in developing industrial connections, but they must be balanced against the increasing financial insecurity of universities today and against a monolithic dependence on an often unsympathetic government.[16]

A connection between the university and an industrial corporation will not necessarily compromise academic integrity, though no thinking person should deny that such a connection could, in subtle and powerful ways, distort the search for truth. These connections will inevitably challenge the commitment to academic integrity. The dangers demand a careful sculpturing of conditions. The pursuit of knowledge – when linked with technology, power, and finance – can never be totally free of outside influences. The whole point of a university is to offer the environment within which the smothering dominance of such influences can be broken.

The introduction of a powerful new technology exerts effects far beyond the immediate targets for which the technology is designed. The connection of biomedical technologies to corporate ventures may significantly transform the university. How should this transformation of one of society's fundamental institutions be controlled? The meeting of the heads of major North American universities in March 1982 at Pajaro Dunes, California,[17] was only the first of many rounds of discussions that will be essential to create a new university-industrial combination that will protect and enhance, not enslave, science and university education.

Conclusion

How can society be prepared to make decisions about technologies that will dominate our lives for years to come? Big and pervasive technologies, such as those in the fields of energy and communications, tend to be irrevocable once introduced into society. The more pervasive a technology, the more ignorant we are during its nascent stage of the range of changes it will bring about. The technologies examined in this study promise to be pervasive, even if one may argue about their effects.

Project inquiries, consensus conferences, science courts, citizen review boards, and royal commissions of inquiry are examples of democratic procedures that can prepare society for the introduction of powerful new technologies. Canada might do well to establish a forum similar to the Education, Science, and Arts Committee of the House of Commons in England or a body similar to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research in the U.S. The British government has also established a committee to consider the implications of in vitro fertilization. Each of these approaches undoubtedly contains valuable ideas, but one has to question the degree of societal preparation they will afford and of societal control they will permit.

We have generally failed to create instruments of democratic deliberation to match the speed and power of the technologies we presume to control. The challenge remains: follow the course of least resistance, or work mightily to adapt the exigencies of a technological society to the principles, structures, procedures, and schedules of a democratic society.

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